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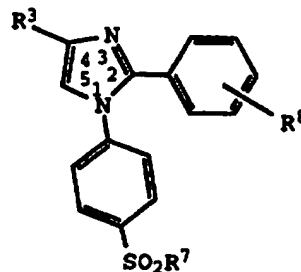
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(54) Title: 1,2-SUBSTITUTED IMIDAZOLYL COMPOUNDS FOR THE TREATMENT OF INFLAMMATION

(57) Abstract

A class of imidazolyl compounds is described for use in treating inflammation. Compounds of particular interest are defined by formula (II), wherein R³ is a radical selected from hydrido, alkyl, haloalkyl, aralkyl, heterocycloalkyl, acyl, cyano, alkoxy, alkylthio, alkylthioalkyl, alkylsulfonyl, cycloalkyloxy, cycloalkyloxyalkyle, cycloalkylthio, cycloalkylthioalkyl, cycloalkylsulfonyl, cyanoalkyl, cycloalkylsulfonylalkyl, haloalkylsulfonyl, azidoalkyl, arylsulfonyl, halo, hydroxyalkyl, alkoxyalkyl, arylthio, alkylcarbonyl, arylcarbonyl, alkylcarbonyl, arylloxy, heterocycloalkylcarbonyl, alkylaminoalkyl, N-arylaminalkyl, N-alkyl-N-arylaminalkyl, carboxyalkyl, alkoxy-carbonylalkyl, alkoxy-carbonyl, haloalkylcarbonyl, aminocarbonyl, alkylaminocarbonylalkyl, aralkylthio, heteroarylalkoxyalkyl, heteroarylalkoxyalkyl, aralkoxy, heteroarylthioalkyl, heteroarylalkoxy, heteroarylthio, arylthioalkyl, arylthioalkyl, aralkylthioalkyl, aralkoxyalkyl, aryl and heteroaryl, wherein the aryl and heteroaryl radicals are optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkyl, cyano, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl and haloalkoxy; wherein R⁷ is a radical selected from alkyl and amino; and wherein R⁸ is one or more radicals selected from hydrido, halo, alkyl, haloalkyl, alkoxy, amino, haloalkoxy, cyano, carboxyl, hydroxyl, hydroxyalkyl, alkoxyalkyl, alkylamino, nitro and alkylthio.



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| GA | Gabon | | | | |

**1,2-SUBSTITUTED IMIDAZOLYL COMPOUNDS
FOR THE TREATMENT OF INFLAMMATION**

FIELD OF THE INVENTION

5

This invention is in the field of antiinflammatory pharmaceutical agents and specifically relates to compounds, compositions and methods for treating inflammation and inflammation-associated disorders, such as arthritis.

BACKGROUND OF THE INVENTION

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG₂, PGH₂ and PGE₂, has been a common target of antiinflammatory drug discovery. However, common non-steroidal antiinflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 (COX-2)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces

inflammation and produces fewer and less drastic side effects.

The references below that disclose antiinflammatory activity, show continuing efforts to find a safe and effective antiinflammatory agent. The novel imidazoles disclosed herein are such safe and also effective antiinflammatory agents furthering such efforts. The invention compounds are found to show usefulness in vivo as antiinflammatory agents with minimal side effects.

10 The substituted imidazoles disclosed herein preferably selectively inhibit cyclooxygenase-2 over cyclooxygenase-1.

Diaryl oxazoles have been described in WO patent publication WO94/27980 as having antiinflammatory activity. Substituted 4,5-diarylimidazoles have been described in WO95/00501 and in copending U.S. application 08/281,903.

2-Alkylimidazoles have been described as having angiotensin II activity. For example, see U.S. Patent No. 5,185,351 and WO 91/00277.

U.S. Patent No. 5,207,820 to Wriede et al. describes 1-arylimidazole carboxylic esters as herbicide safeners. Specifically, ethyl [1-[2,6-dinitro-4-(methylsulfonyl)phenyl]-2-methyl-1H-imidazol-3-yl]carboxylate is described.

WO 93/14082, published July 22, 1993, describes 1-pyridyl-2-phenyl-imidazole derivatives for the treatment of interleukin-1 mediated diseases. 1-(4-Pyridyl)-2-(4-fluorophenyl)-4-methylimidazole is described. WO 95/02591, published January 26, 1995, describe trisubstituted imidazoles for the treatment of cytokine mediated diseases.

U.S. Patent No. 3,487,087, to Sarett et al., describes a method of nitration of imidazoles and specifically 1-methyl-2-[4-(methylsulfonyl)phenyl]-5-nitroimidazole.

U.S. Patent No. 5,112,532, to Ninomiya et al., describes imidazoles as an organic non-linear optical material. Specifically, 4-(4-hydroxyphenyl)-2-[2-formyl-4-(methylsulfonyl)phenyl]imidazole is described.

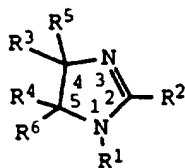
5 U.S. Patent Nos. 3,682,949 and 3,719,759, to Sarett et al., describe 2-aryl-nitroimidazoles as agents for the treatment of parasites and bacteria. Specifically, 1-(2-hydroxyethyl)-2-(4-sulfonamidophenyl)-5-nitroimidazole is described.

10 U.S. Patent No. 4,822,805, to Takasugi et al., describes pyridylimidazoles as antiinflammatory agents. Specifically, 2-[2-methoxy-4-(methylsulfonyl)phenyl]-4-methyl-5-(3-pyridyl)imidazole is described.

15 The invention's imidazolyl compounds are found to show usefulness *in vivo* as antiinflammatory agents with minimal side effects.

DESCRIPTION OF THE INVENTION

20 A class of substituted imidazolyl compounds useful in treating inflammation-related disorders is defined by Formula I:



(I)

25 wherein R¹ and R² are independently selected from aryl, cycloalkyl, cycloalkenyl and heterocyclo, wherein R¹ and R² are optionally substituted at a substitutable position with one or more radicals independently
30 selected from alkylsulfonyl, aminosulfonyl, haloalkylsulfonyl, halo, alkylthio, alkyl, cyano, carboxyl, alkoxycarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, alkoxyalkyl, haloalkoxy, amino, alkylamino, arylamino and nitro;

wherein R^3 is a radical selected from hydrido, alkyl, haloalkyl, aralkyl, heterocycloalkyl, acyl, cyano, alkoxy, alkylthio, alkylthioalkyl, alkylsulfonyl, cycloalkylthio, cycloalkylthioalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, cycloalkyloxy, cycloalkyloxyalkyl, haloalkylsulfonyl, arylsulfonyl, halo, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocycloalkylcarbonyl, cyanoalkyl, azidoalkyl, aminoalkyl, alkylaminoalkyl, N-aryl aminoalkyl, N-alkyl-N-aryl aminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, haloalkylcarbonyl, carboxyl, aminocarbonyl, alkylaminocarbonyl, alkylaminocarbonylalkyl, heteroarylalkoxyalkyl, heteroaryloxyalkyl, heteroarylthioalkyl, aralkoxy, aralkylthio, heteroaralkoxy, heteroaralkylthio, heteroarylalkylthioalkyl, heteroaryloxy, heteroarylthio, arylthioalkyl, aryloxyalkyl, arylthio, aryloxy, aralkylthioalkyl, aralkoxyalkyl, aryl and heterocyclo;

wherein R^4 is a radical selected from hydrido, alkyl and fluoro;

wherein R^5 is selected from hydroxyl and alkoxy;

and

wherein R^6 is hydrido; or wherein R^5 and R^6 together form a double bond;

provided at least one of R^1 and R^2 is substituted with alkylsulfonyl or aminosulfonyl;

or a pharmaceutically-acceptable salt thereof.

Compounds of Formula I would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of the invention would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and

juvenile arthritis. Such compounds of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns and dermatitis. Compounds of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention of colorectal cancer. Compounds of the invention would be useful in treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, conjunctivitis, swelling occurring after injury, myocardial ischemia, and the like. The compounds were also be useful in the treatment of ophthalmic diseases such as retinitis, retinopathies, uveitis, and of acute injury to the eye tissue. The compounds would also be useful for the treatment of certain central nervous system disorders such as alzheimers disease and dementia. The compounds of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These compounds would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis and central nervous system damage resulting from stroke, ischemia and trauma.

Besides being useful for human treatment, these compounds are also useful for treatment of mammals, including horses, dogs, cats, rats, mice, sheep, pigs, etc.

The present compounds may also be used in co-therapies, partially or completely, in place of other conventional antiinflammatories, such as together with steroids, NSAIDs, 5-lipoxygenase inhibitors, LTB₄ antagonists and LTA₄ hydrolase inhibitors.

Suitable LTB₄ inhibitors include, among others, ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, Terumo compound TMK-688, Lilly compounds LY-213024, 264086 and 292728, ONO compound ONO-LB457, Searle compound SC-53228, calcitrol, Lilly compounds LY-210073, LY223982, LY233469, and LY255283, ONO compound ONO-LB-448, Searle compounds SC-41930, SC-50605 and SC-51146, and SK&F compound SKF-104493. Preferably, the LTB₄ inhibitors are selected from ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, and Terumo compound TMK-688.

Suitable 5-LO inhibitors include, among others, masoprocil, tenidap, zileuton, pranlukast, tepoxalin, rilopirox, flezelastine hydrochloride, enazadrem phosphate, and bunaprolast.

The present invention preferably includes compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC₅₀ equal to or less than about 0.2 μ M, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC₅₀ of greater than about 1.0 μ M, and more preferably of greater than 10 μ M. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

A preferred class of compounds consists of those compounds of Formula I wherein R¹ and R² are

independently selected from phenyl, naphthyl, biphenyl, lower cycloalkyl, lower cycloalkenyl and heteroaryl, wherein R¹ and R² are optionally substituted at a substitutable position with one or more radicals

5 independently selected from lower alkylsulfonyl, aminosulfonyl, lower haloalkylsulfonyl, halo, lower alkylthio, lower alkyl, cyano, carboxyl, lower alkoxy, lower alkoxyalkyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower alkoxyalkyl, lower haloalkoxy,

10 amino, lower alkylamino, arylamino and nitro; wherein R³ is a radical selected from hydrido, lower alkyl, lower haloalkyl, lower aralkyl, lower heterocycloalkyl, acyl, cyano, lower alkoxy, lower alkylthio, lower alkylsulfonyl, lower cycloalkyloxy, lower

15 cycloalkyloxyalkyl, lower cycloalkylthio, lower cycloalkylthioalkyl, lower cycloalkylsulfonyl, lower cycloalkylsulfonylalkyl, phenylsulfonyl, lower haloalkylsulfonyl, halo, lower hydroxyalkyl, lower alkoxyalkyl, lower alkylcarbonyl, lower azidoalkyl,

20 lower haloalkylcarbonyl, phenylcarbonyl, lower aralkylcarbonyl, lower heterocycloalkylcarbonyl, lower cyanoalkyl, lower aminoalkyl, lower alkylaminoalkyl, lower N-arylaminoalkyl, lower N-alkyl-N-arylaminoalkyl, lower carboxyalkyl, lower alkoxyalkyl, lower

25 alkoxyalkyl, lower alkylthioalkyl, aminocarbonyl, lower alkylaminocarbonyl, lower alkylaminocarbonylalkyl, lower aralkoxy, lower aralkylthio, lower heteroaralkoxy, lower heteroaralkylthio, lower heteroarylalkoxyalkyl, lower heteroarylalkylthioalkyl, lower

30 heteroaryloxyalkyl, lower heteroarylthioalkyl, lower heteroaryloxy, lower heteroarylthio, lower arylthioalkyl, lower aryloxyalkyl, lower arylthio, lower aryloxy, lower aralkylthioalkyl, lower aralkoxyalkyl, aryl selected from phenyl and naphthyl, and heteroaryl,

35 wherein the aryl and heteroaryl radicals are optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower

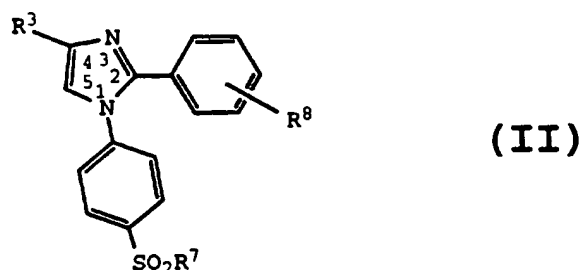
alkylsulfinyl, lower alkyl, cyano, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl and lower haloalkoxy; wherein R⁴ is a radical selected from hydrido, lower alkyl and fluoro; and wherein R⁵ is
5 selected from hydroxyl and lower alkoxy; wherein R⁶ is hydrido; or wherein R⁵ and R⁶ together form a double bond; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula I wherein R¹ and
10 R² are independently selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclohexenyl, benzofuryl, benzodioxolyl, furyl, imidazolyl, thienyl, thiazolyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzimidazolyl, pyrazinyl,
15 indolyl, pyrazolyl and pyridyl, wherein R¹ and R² are optionally substituted at a substitutable position with one or more radicals independently selected from methylsulfonyl, aminosulfonyl, fluoromethylsulfonyl, difluoromethylsulfonyl, fluoro, chloro, bromo,
20 methylthio, methyl, ethyl, isopropyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, fluoromethyl,
25 difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy,
30 methylenedioxy, ethoxy, propoxy, n-butoxy, hydroxymethyl, hydroxyethyl, methoxymethyl, ethoxymethyl, trifluoromethoxy, amino, methylamino, N,N-dimethylamino, phenylamino and nitro; wherein R³ is a radical selected from hydrido, methyl, ethyl, isopropyl,
35 tert-butyl, isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl,

- heptafluoropropyl, difluorochloromethyl,
dichlorofluoromethyl, difluoroethyl, difluoropropyl,
dichloroethyl, dichloropropyl, benzyl, phenylethyl,
phenylpropyl, furylmethyl, morpholinomethyl,
5 pyrrolidinylmethyl, piperazinylmethyl,
piperidinylmethyl, pyridylmethyl, thienylmethyl, formyl,
cyano, methoxy, ethoxy, propoxy, n-butoxy, methylthio,
ethylthio, isopropylthio, methylsulfonyl,
phenylsulfonyl, trifluoromethylsulfonyl, fluoro, chloro,
10 bromo, hydroxymethyl, hydroxyethyl, methoxymethyl,
ethoxymethyl, methylthiomethyl, isopropylthiomethyl,
cyclohexylthiomethyl, benzyloxy, benzylthio,
methylcarbonyl, ethylcarbonyl, phenylcarbonyl,
azidomethyl, trifluoromethylcarbonyl,
15 difluoromethylcarbonyl, fluoromethylcarbonyl,
benzylcarbonyl, cyanomethyl, cyanobutyl, aminomethyl,
methylaminomethyl, N-phenylaminomethyl, N-methyl-N-
phenylaminomethyl, acetyl, propanoyl, butanoyl,
methoxycarbonylmethyl, ethoxycarbonylethyl,
20 methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl,
tert-butoxycarbonyl, propoxycarbonyl, isobutoxycarbonyl,
carboxymethyl, carboxypropyl, aminocarbonyl,
methylaminocarbonyl, N,N-diethylaminocarbonyl, N-
methylaminocarbonylmethyl, pyridyloxy, pyridylthio,
25 phenyloxy, 4-chlorophenoxy, furylmethoxy,
furylmethylthio, thienylmethoxy, quinolylmethoxy,
pyridylmethoxy, 5-phenylpyridyl-2-methoxy,
thienylmethylthio, pyridylmethylthio, benzylthiomethyl,
quinolylmethoxymethyl, furylbutoxyethyl,
30 pyridyloxymethyl, pyridylmethoxymethyl, thienyloxyhexyl,
thienylthiomethyl, pyridylthiohexyl, furyloxymethyl,
furylmethylthiomethyl, quinolylmethylthioethyl,
phenylthiomethyl, 2-chlorophenylthiomethyl, 2,6-
dichlorophenylthiomethyl, 4-methylphenylthiomethyl, 2-
35 isopropylphenylthiomethyl, 2-methylphenylthiomethyl,
phenyloxymethyl, 4-chlorophenyloxymethyl, 4-
methylphenyloxymethyl, benzyloxymethyl, 4-

methoxybenzyloxymethyl, naphthyl, phenyl, thienyl,
 furyl, pyridyl, wherein the thienyl, furyl, pyridyl and
 phenyl radicals are optionally substituted at a
 substitutable position with one or more radicals
 5 selected from fluoro, chloro, bromo, methylthio,
 methylsulfinyl, methyl, ethyl, isopropyl, tert-butyl,
 isobutyl, pentyl, hexyl, cyano, fluoromethyl,
 difluoromethyl, trifluoromethyl, chloromethyl,
 dichloromethyl, trichloromethyl, pentafluoroethyl,
 10 heptafluoropropyl, difluorochloromethyl,
 dichlorofluoromethyl, difluoroethyl, difluoropropyl,
 dichloroethyl, dichloropropyl, hydroxyl, methoxy,
 methylenedioxy, ethoxy, propoxy, n-butoxy,
 hydroxymethyl, hydroxyethyl and trifluoromethoxy;
 15 wherein R^4 is a radical selected from hydrido, methyl,
 ethyl, and fluoro; and wherein R^5 is selected from
 hydroxyl, methoxy, ethoxy, propoxy and n-butoxy; wherein
 R^6 is hydrido; or wherein R^5 and R^6 together form a
 double bond; or a pharmaceutically-acceptable salt
 20 thereof.

Within Formula I there is a subclass of compounds
 of high interest represented by Formula II:



25 wherein R^3 is a radical selected from hydrido, alkyl,
 haloalkyl, aralkyl, heterocycloalkyl, acyl, cyano,
 alkoxy, alkylthio, alkylthioalkyl, alkylsulfonyl,
 cycloalkyloxy, cycloalkyloxyalkyl, cycloalkylthio,
 30 cycloalkylthioalkyl, cycloalkylsulfonyl,
 cycloalkylsulfonylalkyl, haloalkylsulfonyl,
 arylsulfonyl, halo, hydroxyalkyl, alkoxyalkyl,

alkylcarbonyl, arylcarbonyl, aralkylcarbonyl,
heterocycloalkylcarbonyl, cyanoalkyl, alkylaminoalkyl,
N-arylaminoalkyl, N-alkyl-N-arylaminoalkyl,
carboxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl,
5 haloalkylcarbonyl, aminocarbonyl, azidoalkyl,
alkylaminocarbonylalkyl, heteroarylalkoxyalkyl,
heteroaryloxyalkyl, heteroarylthioalkyl, aralkoxy,
aralkylthio, heteroaralkoxy, heteroaralkylthio,
heteroarylalkylthioalkyl, heteroaryloxy, heteroarylthio,
10 arylthioalkyl, aryloxyalkyl, arylthio, aryloxy,
aralkylthioalkyl, aralkoxyalkyl, aryl and heteroaryl,
wherein the aryl and heteroaryl radicals are optionally
substituted at a substitutable position with one or more
radicals selected from halo, alkylthio, alkylsulfinyl,
15 alkyl, cyano, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl
and haloalkoxy; wherein R⁷ is a radical selected from
alkyl, haloalkyl and amino; and wherein R⁸ is one or
more radicals selected from hydrido, halo, alkyl,
haloalkyl, alkoxy, amino, haloalkoxy, cyano, carboxyl,
20 hydroxyl, hydroxyalkyl, alkoxylalkyl, alkylamino, nitro
and alkylthio; or a pharmaceutically-acceptable salt
thereof.

A preferred class of compounds consists of those
compounds of Formula II wherein R³ is a radical selected
25 from hydrido, lower alkyl, lower haloalkyl, lower
aralkyl, lower heterocycloalkyl, acyl, cyano, lower
alkoxy, lower alkylthio, lower alkylsulfonyl,
phenylsulfonyl, lower haloalkylsulfonyl, lower
cycloalkyloxy, lower cycloalkyloxyalkyl, lower
30 cycloalkylthio, lower cycloalkylthioalkyl, lower
cycloalkylsulfonyl, lower cycloalkylsulfonylalkyl, halo,
lower hydroxyalkyl, lower alkoxyalkyl, lower
alkylcarbonyl, lower haloalkylcarbonyl, phenylcarbonyl,
lower aralkylcarbonyl, lower heterocycloalkylcarbonyl,
35 lower cyanoalkyl, lower azidoalkyl, lower
alkylaminoalkyl, lower N-arylaminoalkyl, lower N-alkyl-
N-arylaminoalkyl, lower carboxyalkyl, lower

- alkoxycarbonylalkyl, lower alkoxycarbonyl, lower
alkylthioalkyl, aminocarbonyl, lower
alkylaminocarbonylalkyl, lower aralkoxy, lower
aralkylthio, lower heteroaralkoxy, lower
5 heteroaralkylthio, lower heteroarylalkoxyalkyl, lower
heteroarylalkylthioalkyl, lower heteroaryloxyalkyl,
lower heteroarylthioalkyl, lower heteroaryloxy, lower
heteroarylthio, lower arylthioalkyl, lower aryloxyalkyl,
lower arylthio, lower aryloxy, lower aralkylthioalkyl,
10 lower aralkoxyalkyl, aryl selected from phenyl and
naphthyl, 5 or 6 membered heteroaryl, wherein the aryl
and heteroaryl radicals are optionally substituted at a
substitutable position with one or more radicals
selected from halo, lower alkylthio, lower
15 alkylsulfinyl, lower alkyl, cyano, lower haloalkyl,
hydroxyl, lower alkoxy, lower hydroxyalkyl and lower
haloalkoxy; wherein R⁷ is a radical selected from lower
alkyl, lower haloalkyl and amino; and wherein R⁸ is a
radical selected from hydrido, halo, lower alkyl, lower
20 haloalkyl, lower alkoxy, amino, lower haloalkoxy, cyano,
carboxyl, hydroxyl, lower hydroxyalkyl, lower
alkoxyalkyl, lower alkylamino, nitro and lower
alkylthio; or a pharmaceutically-acceptable salt
thereof.
- 25 A class of compounds of particular interest
consists of those compounds of Formula II wherein R³ is
a radical selected from hydrido, methyl, ethyl,
isopropyl, tert-butyl, isobutyl, pentyl, hexyl,
fluoromethyl, difluoromethyl, trifluoromethyl,
30 chloromethyl, dichloromethyl, trichloromethyl,
pentafluoroethyl, heptafluoropropyl,
difluorochloromethyl, dichlorofluoromethyl,
difluoroethyl, difluoropropyl, dichloroethyl,
dichloropropyl, benzyl, phenylethyl, phenylpropyl,
35 furylmethyl, morpholinomethyl, pyrrolidinylmethyl,
piperazinylmethyl, piperidinylmethyl, pyridylmethyl,
thienylmethyl, formyl, cyano, methoxy, ethoxy, propoxy,

n-butoxy, methylthio, ethylthio, isopropylthio, methylsulfonyl, phenylsulfonyl, trifluoromethylsulfonyl, fluoro, chloro, bromo, hydroxymethyl, hydroxyethyl, methoxymethyl, ethoxymethyl, methylthiomethyl, 5 isopropylthiomethyl, cyclohexylthiomethyl, benzyloxy, benzylthio, methylcarbonyl, phenylcarbonyl, trifluoromethylcarbonyl, difluoromethylcarbonyl, fluoromethylcarbonyl, benzylcarbonyl, cyanomethyl, cyanobutyl, azidomethyl, methylaminomethyl, N- 10 phenylaminomethyl, N-methyl-N-phenylaminomethyl, acetyl, propanoyl, butanoyl, methoxycarbonylmethyl, ethoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, propoxycarbonyl, carboxymethyl, carboxypropyl, 15 aminocarbonyl, N-methylaminocarbonylmethyl, pyridyloxy, pyridylthio, phenyloxy, 4-chlorophenoxy, furylmethoxy, furylmethylthio, thienylmethoxy, quinolylmethoxy, pyridylmethoxy, 5-phenylpyridyl-2-methoxy, thienylmethylthio, pyridylmethylthio, benzylthiomethyl, 20 quinolylmethoxymethyl, furylbutoxyethyl, pyridyloxymethyl, pyridylmethoxymethyl, thienyloxyhexyl, thienylthiomethyl, pyridylthiohexyl, furyloxymethyl, furylmethylthiomethyl, quinolylmethylthioethyl, phenylthiomethyl, 2-chlorophenylthiomethyl, 2,6- 25 dichlorophenylthiomethyl, 4-methylphenylthiomethyl, 2-isopropylphenylthiomethyl, 2-methylphenylthiomethyl, phenyloxymethyl, 4-chlorophenyloxymethyl, 4-methylphenyloxymethyl, benzyloxymethyl, 4-methoxybenzyloxymethyl, naphthyl, phenyl, thienyl, 30 furyl, pyridyl, wherein the thienyl, furyl, pyridyl and phenyl radicals are optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methylsulfinyl, methyl, ethyl, isopropyl, tert-butyl, 35 isobutyl, pentyl, hexyl, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl,

heptafluoropropyl, difluorochloromethyl,
dichlorofluoromethyl, difluoroethyl, difluoropropyl,
dichloroethyl, dichloropropyl, hydroxyl, methoxy,
methylenedioxy, ethoxy, propoxy, n-butoxy,
5 hydroxymethyl, hydroxyethyl and trifluoromethoxy;
wherein R⁷ is methyl or amino; and wherein R⁸ is a
radical selected from hydrido, methylsulfonyl, fluoro,
chloro, bromo, methylthio, methyl, ethyl, isopropyl,
tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl,
10 methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl,
tert-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl,
isobutoxycarbonyl, pentoxycarbonyl, fluoromethyl,
difluoromethyl, trifluoromethyl, chloromethyl,
dichloromethyl, trichloromethyl, pentafluoroethyl,
15 heptafluoropropyl, difluorochloromethyl,
dichlorofluoromethyl, difluoroethyl, difluoropropyl,
dichloroethyl, dichloropropyl, hydroxyl, methoxy,
methylenedioxy, ethoxy, propoxy, n-butoxy,
hydroxymethyl, hydroxyethyl, methoxymethyl,
20 ethoxymethyl, trifluoromethoxy, amino, methylamino, N,N-
dimethylamino, phenylamino and nitro; or a
pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular
interest within Formula II consists of compounds and
25 pharmaceutically-acceptable salts thereof as follows:

2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-
(trifluoromethyl)-1H-imidazole;
2-(4-chlorophenyl)-4-[(4-methylphenoxy)methyl]-1-[4-
30 (methylsulfonyl)phenyl]-1H-imidazole;
2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-
[(methylthio)methyl]-1H-imidazole;
1,2-bis[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-
1H-imidazole;
35 4-[2-(3,4-difluorophenyl)-4-(trifluoromethyl)-1H-
imidazol-1-yl]benzenesulfonamide;

- 4-[2-(3-bromo-4-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-carboxaldehyde;
5 2-(4-chlorophenyl)-4-[[4-(methylphenyl)thiomethyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
2-(3-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
2-(4-chlorophenyl)-4-fluoromethyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
10 2-(2-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(phenylmethoxymethyl)-1H-imidazole;
15 4-[2-(2-fluorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
N,N-dimethyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]benzenamine;
2-(4-chlorophenyl)-4-[[1-(methylethyl)thio]methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
20 2-(4-chlorophenyl)-4-[[1-(cyclohexyl)thio]methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
1-[4-(methylsulfonyl)phenyl]-2-[3-(trifluoromethyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
25 2-[3-(methoxymethyl)phenyl]-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
2-fluoro-N,N-dimethyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]benzeneamine;
30 2-(3-bromophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
4-[4-(trifluoromethyl)-2-[3-(trifluoromethyl)phenyl]-1H-imidazol-1-yl]benzenesulfonamide;
35 2-(4-chlorophenyl)-4-[[2-(2-chlorophenyl)thio]methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

- 1-[4-(methylsulfonyl)phenyl]-2-(3-nitrophenyl)-4-(trifluoromethyl)-1H-imidazole;
2-(4-chlorophenyl)-4-[[2-methylphenyl]thio]methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
5 N-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]benzenamine;
3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]benzeneamine;
N,N-dimethyl-3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]benzenamine;
10 N-methyl-3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]benzenamine;
2-fluoro-N-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]benzeneamine;
15 2-(4-chlorophenyl)-4-[[2,6-dichlorophenyl]thio]methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
2-(4-chlorophenyl)-4-[[2-(1-methylethyl)phenyl]thio]methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
20 1-[2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazol-4-yl]ethanone;
1-[4-(methylsulfonyl)phenyl]-2-[3-(methylthio)phenyl]-4-(trifluoromethyl)-1H-imidazole;
25 4-[2-(3-bromophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
2-(3-chloro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
30 4-[2-(3-chloro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-acetonitrile;
2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
35

- 2-(3-fluoro-5-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 5 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-acetic acid;
- 4-[2-(3-fluoro-5-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 10 2-(4-chlorophenyl)-4-trifluoromethyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(4-chlorophenyl)-4-difluoromethyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(4-chlorophenyl)-4-methyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 15 2-(4-chlorophenyl)-4-ethyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(4-chlorophenyl)-4-phenyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 20 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(4-chlorophenyl)-4-(4-bromophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(4-chlorophenyl)-4-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 25 2-(4-chlorophenyl)-4-(2-naphthyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(4-chlorophenyl)-4-[4-(trifluoromethoxy)phenyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 30 2-(4-chlorophenyl)-4-(3-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(4-chlorophenyl)-4-(3-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(4-chlorophenyl)-4-(4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 35 2-(4-chlorophenyl)-4-phenoxyethyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

- 2-(4-chlorophenyl)-4-(4-chlorophenoxy)methyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
2-(4-chlorophenyl)-4-(4-fluorophenoxy)methyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
5 2-(4-chlorophenyl)-4-phenylthiomethyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
2-(4-chlorophenyl)-4-(N-phenyl-N-methylamino)methyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
2-(4-chlorophenyl)-4-(2-quinolyl)methoxymethyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
10 2-(4-chlorophenyl)-4-methoxymethyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
2-(4-chlorophenyl)-4-(4-methoxybenzyloxy)methyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
15 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-methanol;
2-(4-chlorophenyl)-4-formyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-carbonitrile;
20 2-(4-chlorophenyl)-4-benzyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
2-(4-chlorophenyl)-4-phenylethyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
25 2-(4-chlorophenyl)-4-hexyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
2-(4-chlorophenyl)-4-hexylcarbonyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
2-(4-chlorophenyl)-4-phenylcarbonyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
30 2-(4-chlorophenyl)-4-benzylcarbonyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
2-(4-chlorophenyl)-4-(1-hydroxy-1-phenyl-methyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
35 2-(4-chlorophenyl)-4-(1-hexanol)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

- 2-(4-chlorophenyl)-1-[(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(4-chlorophenyl)-4-octyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 5 2-(4-chlorophenyl)-4-methoxy-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(4-chlorophenyl)-4-butoxy-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(4-chlorophenyl)-4-methylthio-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 10 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethylsulfonyl-1H-imidazole;
- 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethylcarbonyl-1H-imidazole;
- 15 2-(4-chlorophenyl)-4-(2-thienyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(4-chlorophenyl)-4-(3-furyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(4-chlorophenyl)-4-(4-pyridyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 20 2-(4-chlorophenyl)-4-chloro-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(4-chlorophenyl)-4-fluoro-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 25 methyl [2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazol-4-yl]carboxylate;
- [2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazol-4-yl]carboxamide;
- methyl [2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazol-4-yl]carboxamide;
- 30 4-[2-(4-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-difluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 35 4-[2-(4-chlorophenyl)-4-methyl-1H-imidazol-1-yl]benzenesulfonamide;

- 4-[2-(4-chlorophenyl)-4-ethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-chlorophenyl)-4-phenyl-1H-imidazol-1-yl]benzenesulfonamide;
5 4-[2-(4-chlorophenyl)-4-(4-fluorophenyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-chlorophenyl)-4-(4-bromophenyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-chlorophenyl)-4-(4-chlorophenyl)-1H-imidazol-1-yl]benzenesulfonamide;
10 4-[2-(4-chlorophenyl)-4-(2-naphthyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-chlorophenyl)-4-[4-(trifluoromethoxy)phenyl]-1H-imidazol-1-yl]benzenesulfonamide;
15 4-[2-(4-chlorophenyl)-4-(3-chlorophenyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-chlorophenyl)-4-(3-fluorophenyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-chlorophenyl)-4-(4-methoxyphenyl)-1H-imidazol-1-yl]benzenesulfonamide;
20 4-[2-(4-chlorophenyl)-4-phenoxyethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-chlorophenyl)-4-(4-chlorophenoxy)methyl-1H-imidazol-1-yl]benzenesulfonamide;
25 4-[2-(4-chlorophenyl)-4-(4-fluorophenoxy)methyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-chlorophenyl)-4-phenylthiomethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-chlorophenyl)-4-(N-phenyl-N-methylamino)methyl-1H-imidazol-1-yl]benzenesulfonamide;
30 4-[2-(4-chlorophenyl)-4-(2-quinolyl)methoxymethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-chlorophenyl)-4-methoxymethyl-1H-imidazol-1-yl]benzenesulfonamide;
35 4-[2-(4-chlorophenyl)-4-(4-methoxybenzyloxy)methyl-1H-imidazol-1-yl]benzenesulfonamide;

- 4-[2-(4-chlorophenyl)-4-hydroxymethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-formyl-1H-imidazol-1-yl]benzenesulfonamide;
- 5 4-[2-(4-chlorophenyl)-4-cyano-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-benzyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-phenylethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 10 4-[2-(4-chlorophenyl)-4-hexyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-hexylcarbonyl-1H-imidazol-1-yl]benzenesulfonamide;
- 15 4-[2-(4-chlorophenyl)-4-phenylcarbonyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-benzylcarbonyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-(1-hydroxy-1-phenyl-methyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 20 4-[2-(4-chlorophenyl)-4-(1-hexanol)-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 25 4-[2-(4-chlorophenyl)-4-octyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-methoxy-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-butoxy-1H-imidazol-1-yl]benzenesulfonamide;
- 30 4-[2-(4-chlorophenyl)-4-methylthio-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-(2-thienyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 35 4-[2-(4-chlorophenyl)-4-(3-furyl)-1H-imidazol-1-yl]benzenesulfonamide;

- 4-[2-(4-chlorophenyl)-4-(4-pyridyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-chlorophenyl)-4-chloro-1H-imidazol-1-yl]benzenesulfonamide;
5 4-[2-(4-chlorophenyl)-4-fluoro-1H-imidazol-1-yl]benzenesulfonamide;
[2-(4-chlorophenyl)-1-[4-(aminosulfonyl)phenyl]-1H-imidazol-4-yl]carboxylic acid;
methyl[2-(4-chlorophenyl)-1-[4-(aminosulfonyl)phenyl]-1H-imidazol-4-yl]carboxylate;
10 [2-(4-chlorophenyl)-1-[4-(aminosulfonyl)phenyl]-1H-imidazol-4-yl]carboxamide;
methyl[2-(4-chlorophenyl)-1-[4-(aminosulfonyl)phenyl]-1H-imidazol-4-yl]carboxamide;
15 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
2-(2-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
2-(4-fluoro-3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
20 2-(4-chloro-3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
25 2-(4-fluoro-3-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
2-(4-chloro-3-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
30 2-(3-fluoro-4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
2-(3-chloro-4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
35

- 2-(3-fluoro-4-methylthiophenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 2-(3-chloro-4-methylthiophenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 2-(4-fluoro-3-methylthiophenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 2-(4-chloro-3-methylthiophenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 2-(3,5-dimethyl-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 2-(3,5-dichloro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 2-(3,5-difluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 2-(3,4-dimethylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 2-(3,5-dichlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(2-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-fluoro-3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chloro-3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-fluoro-3-methoxyphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chloro-3-methoxyphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

- 4-[2-(3-fluoro-4-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(3-chloro-4-methylthiophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
5 4-[2-(3-fluoro-4-methylthiophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-fluoro-3-methylthiophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-chloro-4-methylthiophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
10 4-[2-(3,5-dimethyl-4-methoxyphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(3,5-dichloro-4-methoxyphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
15 4-[2-(3,5-difluoro-4-methoxyphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(3,4-dimethylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(3,5-dichlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
20 ethyl [2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazol-4-yl]carboxylate;
ethyl [1-[4-(aminosulfonyl)phenyl]-2-(4-chlorophenyl)-1H-imidazol-4-yl]carboxylate;
25 1-[4-(methylsulfonyl)phenyl]-2-(4-methylphenyl)-4-trifluoromethyl-1H-imidazole;
1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
1-[4-(methylsulfonyl)phenyl]-2-(4-methyl-3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
30 5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]-1,3-benzodioxole;
1-[4-(methylsulfonyl)phenyl]-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole;
35 1-[4-(methylsulfonyl)phenyl]-2-(3-fluorophenyl)-4-trifluoromethyl-1H-imidazole;

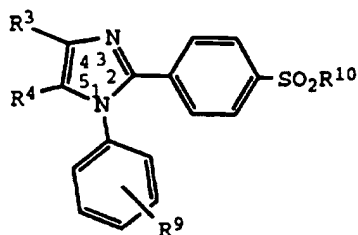
- 1-[4-(methylsulfonyl)phenyl]-2-(4-fluorophenyl)-4-trifluoromethyl-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-(4-methoxy-3-fluorophenyl)-4-trifluoromethyl-1H-imidazole;
- 5 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-[4-(trifluoromethyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 10 1-[4-(methylsulfonyl)phenyl]-2-(4-bromophenyl)-4-trifluoromethyl-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-(2-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 15 1-[4-(methylsulfonyl)phenyl]-2-(4-ethylphenyl)-4-trifluoromethyl-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-(4-butylphenyl)-4-trifluoromethyl-1H-imidazole;
- 20 1-[4-(methylsulfonyl)phenyl]-2-[4-(difluoromethyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-(4-butoxyphenyl)-4-trifluoromethyl-1H-imidazole;
- 25 1-[4-(methylsulfonyl)phenyl]-2-[4-(methylthio)phenyl]-4-trifluoromethyl-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-(4-methoxy-3,5-dichlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-(4-methyl-3,5-difluorophenyl)-4-trifluoromethyl-1H-imidazole;
- 30 1-[4-(methylsulfonyl)phenyl]-2-(2,4-dichlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-(3,4-dichlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 35 1-[4-(methylsulfonyl)phenyl]-2-[4-(trifluoromethyl)phenyl]-4-trifluoromethoxy-1H-imidazole;

- 1-[4-(methylsulfonyl)phenyl]-2-(3,5-dimethyl-4-methoxy-phenyl)-4-trifluoromethyl-1H-imidazole;
1-[4-(methylsulfonyl)phenyl]-2-(3,4-dimethylphenyl)-4-trifluoromethyl-1H-imidazole;
5 1-[4-(methylsulfonyl)phenyl]-2-(4-aminophenyl)-4-trifluoromethyl-1H-imidazole;
4-[2-(4-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
10 4-[2-(4-methyl-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
5-[1-[4-(aminosulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]-1,3-benzodioxole;
15 4-[2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(3-fluorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-fluorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
20 4-[2-(4-methoxy-3-fluorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
25 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-[4-(trifluoromethyl)phenyl]-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-bromophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
30 4-[2-(2-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-ethylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
35 4-[2-(4-butylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

- 4-[2-[4-(difluoromethyl)phenyl]-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
 4-[2-(4-butoxyphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
 5 4-[2-[4-(methylthio)phenyl]-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
 4-[2-(4-methoxy-3,5-dichloro-phenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
 4-[2-(4-methyl-3,5-difluorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
 10 4-[2-(2,4-dichlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
 4-[2-(3,4-dichlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
 15 4-[2-[4-(trifluoromethoxy)phenyl]-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
 4-[2-(3,5-dimethyl-4-methoxy-phenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
 4-[2-(3,4-dimethylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide; and
 20 4-[2-(4-aminophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide.

Within Formula I there is a second subclass of compounds of high interest represented by Formula III:

25



(III)

- wherein R^3 is a radical selected from hydrido, alkyl, haloalkyl, aralkyl, heterocycloalkyl, acyl, cyano, alkoxy, alkylthio, alkylthioalkyl, alkylsulfonyl, cycloalkylthio, cycloalkylthioalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, cycloalkyloxy, cycloalkyloxyalkyl, haloalkylsulfonyl, arylsulfonyl,
- 30

- halo, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocycloalkylcarbonyl, cyanoalkyl, azidoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-alkyl-N-arylaminoalkyl, carboxyalkyl, 5 alkoxycarbonylalkyl, alkoxycarbonyl, haloalkylcarbonyl, aminocarbonyl, N-alkylaminocarbonylalkyl, heteroarylalkoxyalkyl, heteroaryloxyalkyl, heteroarylthioalkyl, aralkoxy, aralkylthio, heteroaralkoxy, heteroaralkylthio, 10 heteroarylalkylthioalkyl, heteroaryloxy, heteroarylthio, arylthioalkyl, aryloxyalkyl, arylthio, aryloxy, aralkylthioalkyl, aralkoxyalkyl, aryl and heteroaryl; wherein the aryl and heteroaryl radicals are optionally substituted at a substitutable position with one or more 15 radicals selected from halo, alkylthio, alkylsulfinyl, alkyl, cyano, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl and haloalkoxy; wherein R⁴ is a radical selected from hydrido, alkyl and fluoro; wherein R⁹ is one or more radicals selected from hydrido, halo, alkyl, haloalkyl, 20 alkoxy, amino, haloalkoxy, cyano, carboxyl, hydroxyl, hydroxyalkyl, alkoxyalkyl, alkylamino, nitro and alkylthio; and wherein R¹⁰ is a radical selected from alkyl, haloalkyl and amino; or a pharmaceutically-acceptable salt thereof.
- 25 A preferred class of compounds consists of those compounds of Formula III wherein R³ is a radical selected from hydrido, lower alkyl, lower haloalkyl, lower aralkyl, lower heterocycloalkyl, lower heteroaralkyl, acyl, cyano, lower alkoxy, lower 30 alkylthio, lower alkylsulfonyl, phenylsulfonyl, lower haloalkylsulfonyl, halo, lower hydroxyalkyl, lower alkoxyalkyl, lower alkylcarbonyl, lower haloalkylcarbonyl, phenylcarbonyl, lower aralkylcarbonyl, lower cyanoalkyl, lower azidoalkyl, 35 lower alkylaminoalkyl, lower N-arylaminoalkyl, lower N-alkyl-N-arylaminoalkyl, lower carboxyalkyl, lower alkoxycarbonylalkyl, lower alkoxycarbonyl, lower

- alkylthioalkyl, aminocarbonyl, lower
alkylaminocarbonylalkyl, lower aralkoxy, lower
aralkylthio, lower heteroaralkoxy, lower
heteroaralkylthio, lower heteroarylalkoxyalkyl, lower
5 heteroarylalkylthioalkyl, lower heteroaryloxyalkyl,
lower heteroarylthioalkyl, lower heteroaryloxy, lower
heteroarylthio, lower arylthioalkyl, lower aryloxyalkyl,
lower arylthio, lower aryloxy, lower aralkylthioalkyl,
lower aralkoxyalkyl, aryl selected from phenyl and
10 naphthyl, 5 or 6 membered heteroaryl, wherein the aryl
and heteroaryl radicals are optionally substituted at a
substitutable position with one or more radicals
selected from halo, lower alkylthio, lower
alkylsulfinyl, lower alkyl, cyano, lower haloalkyl,
15 hydroxyl, lower alkoxy, lower hydroxyalkyl and lower
haloalkoxy; wherein R^4 is a radical selected from
hydrido, lower alkyl and fluoro; wherein R^9 is a radical
selected from hydrido, halo, lower alkyl, lower
haloalkyl, lower alkoxy, amino, lower haloalkoxy, cyano,
20 carboxyl, hydroxyl, lower hydroxyalkyl, lower
alkoxyalkyl, lower alkylamino, nitro and lower
alkylthio; and wherein R^{10} is a radical selected from
lower alkyl, lower haloalkyl and amino; or a
pharmaceutically-acceptable salt thereof.
- 25 A class of compounds of particular interest
consists of those compounds of Formula III wherein R^3 is
a radical selected from hydrido, methyl, ethyl,
isopropyl, tert-butyl, isobutyl, pentyl, hexyl,
fluoromethyl, difluoromethyl, trifluoromethyl,
30 chloromethyl, dichloromethyl, trichloromethyl,
pentafluoroethyl, heptafluoropropyl,
difluorochloromethyl, dichlorofluoromethyl,
difluoroethyl, difluoropropyl, dichloroethyl,
dichloropropyl, benzyl, phenylethyl, phenylpropyl,
35 furylmethyl, morpholinomethyl, pyrrolidinylmethyl,
piperazinylmethyl, piperidinylmethyl, pyridylmethyl,
thienylmethyl, formyl, cyano, methoxy, ethoxy, propoxy,

- n-butoxy, methylthio, ethylthio, methylsulfonyl, phenylsulfonyl, trifluoromethylsulfonyl, fluoro, chloro, bromo, hydroxymethyl, hydroxyethyl, methoxymethyl, ethoxymethyl, methylthiomethyl, benzyloxy, benzylthio, methylcarbonyl, phenylcarbonyl, trifluoromethylcarbonyl, difluoromethylcarbonyl, fluoromethylcarbonyl, benzylcarbonyl, cyanomethyl, cyanobutyl, azidomethyl, methylaminomethyl, N-phenylaminomethyl, N-methyl-N-phenylaminomethyl, acetyl, propanoyl, butanoyl, methoxycarbonylmethyl, ethoxycarbonylethyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, propoxycarbonyl, aminocarbonyl, methylaminocarbonylmethyl, pyridyloxy, pyridylthio, phenyloxy, 4-chlorophenoxy, furylmethoxy, furylmethylthio, thienylmethoxy, quinolylmethoxy, pyridylmethoxy, 5-phenylpyridyl-2-methoxy, thienylmethylthio, pyridylmethylthio, quinolylmethoxymethyl, furylbutoxyethyl, pyridyloxymethyl, pyridylmethoxymethyl, thienyloxyhexyl, thienylthiomethyl, pyridylthiohexyl, furyloxymethyl, furylmethylthiomethyl, quinolylmethylthioethyl, phenylthiomethyl, phenyloxymethyl, 4-chlorophenyloxymethyl, benzyloxymethyl, 4-methoxybenzyloxymethyl, naphthyl, phenyl, thienyl, furyl, pyridyl, wherein the thienyl, furyl, pyridyl and phenyl radicals are optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methylsulfinyl, methyl, ethyl, isopropyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, hydroxymethyl, hydroxyethyl and trifluoromethoxy;

wherein R⁴ is a radical selected from hydrido, methyl, ethyl and fluoro; wherein R⁹ is a radical selected from hydrido, fluoro, chloro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, methoxy, ethoxy, isopropoxy, *tert*-butoxy, propoxy, butoxy, isobutoxy, pentoxy, methylenedioxy, amino, trifluoromethoxy, cyano, carboxyl, hydroxyl, nitro, hydroxymethyl, methoxymethyl, ethoxymethyl, methylamino, methylthio, ethylthio, propylthio and butylthio; and wherein R¹⁰ is methyl, fluoromethyl or amino, or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula III consists of compounds and pharmaceutically-acceptable salts thereof as follows:

- 1-(4-chlorophenyl)-4-trifluoromethyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
1-(4-chlorophenyl)-4-difluoromethyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
1-(4-chlorophenyl)-4-methyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
1-(4-chlorophenyl)-4-ethyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
1-(4-chlorophenyl)-4-phenyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
1-(4-chlorophenyl)-4-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
1-(4-chlorophenyl)-4-(4-bromophenyl)-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
1-(4-chlorophenyl)-4-(4-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;

- 1-(4-chlorophenyl)-4-(2-naphthyl)-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-[4-(trifluoromethoxy)phenyl]-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 5 1-(4-chlorophenyl)-4-(3-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-(3-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-(4-methoxyphenyl)-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 10 1-(4-chlorophenyl)-4-phenoxyethyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-(4-chlorophenoxy)methyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 15 1-(4-chlorophenyl)-4-(4-fluorophenoxy)methyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-phenylthiomethyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-(N-phenyl-N-methylamino)methyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 20 1-(4-chlorophenyl)-4-(2-quinolyl)methoxymethyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-methoxymethyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 25 1-(4-chlorophenyl)-4-(4-methoxybenzyloxy)methyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-hydroxymethyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-formyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 30 1-(4-chlorophenyl)-4-cyano-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-benzyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 35 1-(4-chlorophenyl)-4-phenylethyl-2-[4-(methylsulfonyl)phenyl]-1H-imidazole;

- 1-(4-chlorophenyl)-4-hexyl-2-[4-(methylsulfonyl)phenyl]-
1H-imidazole;
- 1-(4-chlorophenyl)-4-hexylcarbonyl-2-[4-
(methylsulfonyl)phenyl]-1H-imidazole;
- 5 1-(4-chlorophenyl)-4-phenylcarbonyl-2-[4-
(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-benzylcarbonyl-2-[4-
(methylsulfonyl)phenyl]-1H-imidazole;
- 10 1-(4-chlorophenyl)-4-(1-hydroxy-2-phenyl-methyl)-2-[4-
(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-(1-hexanol)-2-[4-
(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-2-[(methylsulfonyl)phenyl]-1H-
imidazole;
- 15 1-(4-chlorophenyl)-4-octyl-2-[4-(methylsulfonyl)phenyl]-
1H-imidazole;
- 1-(4-chlorophenyl)-4-methoxy-2-[4-
(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-butoxy-2-[4-
(methylsulfonyl)phenyl]-1H-imidazole;
- 20 1-(4-chlorophenyl)-4-methylthio-2-[4-
(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-(2-thienyl)-2-[4-
(methylsulfonyl)phenyl]-1H-imidazole;
- 25 1-(4-chlorophenyl)-4-(3-furyl)-2-[4-
(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-(4-pyridyl)-2-[4-
(methylsulfonyl)phenyl]-1H-imidazole;
- 1-(4-chlorophenyl)-4-chloro-2-[4-
(methylsulfonyl)phenyl]-1H-imidazole;
- 30 1-(4-chlorophenyl)-4-fluoro-2-[4-
(methylsulfonyl)phenyl]-1H-imidazole;
- [1-(4-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]-1H-
imidazol-4-yl]carboxylic acid;
- 35 methyl[1-(4-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]-
1H-imidazol-4-yl]carboxylate;

- [1-(4-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]-1H-imidazol-4-yl]carboxamide;
methyl[1-(4-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]-1H-imidazol-4-yl]carboxamide;
- 5 4-[1-(4-chlorophenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-difluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-methyl-1H-imidazol-2-yl]benzenesulfonamide;
- 10 4-[1-(4-chlorophenyl)-4-ethyl-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-phenyl-1H-imidazol-2-yl]benzenesulfonamide;
- 15 4-[1-(4-chlorophenyl)-4-(4-fluorophenyl)-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-(4-bromophenyl)-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-(4-chlorophenyl)-1H-imidazol-2-yl]benzenesulfonamide;
- 20 4-[1-(4-chlorophenyl)-4-(2-naphthyl)-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-[4-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]benzenesulfonamide;
- 25 4-[1-(4-chlorophenyl)-4-(3-chlorophenyl)-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-(3-fluorophenyl)-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-(4-methoxyphenyl)-1H-imidazol-2-yl]benzenesulfonamide;
- 30 4-[1-(4-chlorophenyl)-4-phenoxyethyl-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-(4-chlorophenoxy)methyl-1H-imidazol-2-yl]benzenesulfonamide;
- 35 4-[1-(4-chlorophenyl)-4-(4-fluorophenoxy)methyl-1H-imidazol-2-yl]benzenesulfonamide;

- 4-[1-(4-chlorophenyl)-4-phenylthiomethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-(N-phenyl-N-methylamino)methyl-1H-imidazol-2-yl]benzenesulfonamide;
- 5 4-[1-(4-chlorophenyl)-4-(2-quinolyl)methoxymethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-methoxymethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-(4-methoxybenzyloxy)methyl-1H-imidazol-2-yl]benzenesulfonamide;
- 10 4-[1-(4-chlorophenyl)-4-hydroxymethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-formyl-1H-imidazol-2-yl]benzenesulfonamide;
- 15 4-[1-(4-chlorophenyl)-4-cyano-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-benzyl-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-phenylethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 20 4-[1-(4-chlorophenyl)-4-hexyl-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-hexylcarbonyl-1H-imidazol-2-yl]benzenesulfonamide;
- 25 4-[1-(4-chlorophenyl)-4-phenylcarbonyl-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-benzylcarbonyl-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-(1-hydroxy-2-phenyl-methyl)-1H-imidazol-2-yl]benzenesulfonamide;
- 30 4-[1-(4-chlorophenyl)-4-(1-hexanol)-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-1H-imidazol-2-yl]benzenesulfonamide;
- 35 4-[1-(4-chlorophenyl)-4-octyl-1H-imidazol-2-yl]benzenesulfonamide;

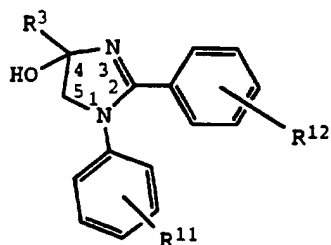
- 4-[1-(4-chlorophenyl)-4-methoxy-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-butoxy-1H-imidazol-2-yl]benzenesulfonamide;
5 4-[1-(4-chlorophenyl)-4-methylthio-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-(3-thienyl)-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-(2-furyl)-1H-imidazol-2-yl]benzenesulfonamide;
10 4-[1-(4-chlorophenyl)-4-(3-pyridyl)-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-chloro-1H-imidazol-2-yl]benzenesulfonamide;
15 4-[1-(4-chlorophenyl)-4-fluoro-1H-imidazol-2-yl]benzenesulfonamide;
[1-(4-chlorophenyl)-2-[4-(aminosulfonyl)phenyl]-1H-imidazol-4-yl]carboxylic acid;
methyl[1-(4-chlorophenyl)-2-[4-(aminosulfonyl)phenyl]-1H-imidazol-4-yl]carboxylate;
20 [1-(4-chlorophenyl)-2-[4-(aminosulfonyl)phenyl]-1H-imidazol-4-yl]carboxamide;
methyl[1-(4-chlorophenyl)-2-[4-(aminosulfonyl)phenyl]-1H-imidazol-4-yl]carboxamide;
25 2-[4-(methylsulfonyl)phenyl]-1-(4-methylphenyl)-4-trifluoromethyl-1H-imidazole;
2-[4-(methylsulfonyl)phenyl]-1-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
2-[4-(methylsulfonyl)phenyl]-2-(4-methyl-3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
30 5-[2-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-1-yl]-1,3-benzodioxole;
2-[4-(methylsulfonyl)phenyl]-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole;
35 2-[4-(methylsulfonyl)phenyl]-1-(3-fluorophenyl)-4-trifluoromethyl-1H-imidazole;

- 2-[4-(methylsulfonyl)phenyl]-1-(4-fluorophenyl)-4-trifluoromethyl-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(4-methoxy-3-fluorophenyl)-4-trifluoromethyl-1H-imidazole;
- 5 2-[4-(methylsulfonyl)phenyl]-1-phenyl-4-trifluoromethyl-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-[4-(trifluoromethyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 10 2-[4-(methylsulfonyl)phenyl]-1-(4-bromophenyl)-4-trifluoromethyl-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(2-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 15 2-[4-(methylsulfonyl)phenyl]-1-(4-ethylphenyl)-4-trifluoromethyl-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(4-butylphenyl)-4-trifluoromethyl-1H-imidazole;
- 20 2-[4-(methylsulfonyl)phenyl]-1-[4-(difluoromethyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(4-butoxyphenyl)-4-trifluoromethyl-1H-imidazole;
- 25 2-[4-(methylsulfonyl)phenyl]-1-[4-(methylthio)phenyl]-4-trifluoromethyl-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(4-methoxy-3,5-dichlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(4-methyl-3,5-difluorophenyl)-4-trifluoromethyl-1H-imidazole;
- 30 2-[4-(methylsulfonyl)phenyl]-1-(2,4-dichlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(3,4-dichlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 35 2-[4-(methylsulfonyl)phenyl]-1-[4-(trifluoromethyl)phenyl]-4-trifluoromethoxy-1H-imidazole;

- 2-[4-(methylsulfonyl)phenyl]-1-(3,5-dimethyl-4-methoxy-phenyl)-4-trifluoromethyl-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(3,4-dimethylphenyl)-4-trifluoromethyl-1H-imidazole;
- 5 2-[4-(methylsulfonyl)phenyl]-1-(4-aminophenyl)-4-trifluoromethyl-1H-imidazole;
- 4-[1-(4-methylphenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 10 4-[1-(4-methyl-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 5-[2-[4-(aminosulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-1-yl]-1,3-benzodioxole;
- 15 4-[1-(3-fluorophenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-fluorophenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-methoxy-3-fluorophenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 20 4-[1-phenyl-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 25 4-[1-[4-(trifluoromethyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-bromophenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(2-chlorophenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 30 4-[1-(4-ethylphenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-butylphenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
- 35 4-[1-[4-(difluoromethyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;

- 4-[1-(4-butoxyphenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
 4-[1-[4-(methylthio)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
 5 4-[1-(4-methoxy-3,5-dichloro-phenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
 4-[1-(4-methyl-3,5-difluorophenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
 10 4-[1-(2,4-dichlorophenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
 4-[1-(3,4-dichlorophenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
 4-[1-[4-(trifluoromethoxy)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
 15 4-[1-(3,5-dimethyl-4-methoxy-phenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide;
 4-[1-(3,4-dimethylphenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide; and
 4-[1-(4-aminophenyl)-4-trifluoromethyl-1H-imidazol-2-yl]benzenesulfonamide.

Within Formula I there is a third subclass of compounds of high interest represented by Formula IV:



(IV)

- 25 wherein R³ is selected from alkyl, haloalkyl, alkylsulfonylalkyl, cycloalkylthioalkyl, alkoxycarbonyl, aralkoxyalkyl, aryloxyalkyl, arylthioalkyl, N-aryl-N-alkylaminoalkyl, heteroarylalkoxyalkyl,
 30 heterocyclocarbonyl, heteroaryloxyalkyl, N-alkoxy-N-alkylaminocarbonyl, heteroaralkylthioalkyl, heteroarylthioalkyl and aryl optionally substituted at a substitutable position with halo, alkoxy and haloalkoxy;

and wherein R¹¹ and R¹² are independently selected from hydrido, halo, alkyl, haloalkyl, alkoxy, alkylsulfonyl, haloalkylsulfonyl and sulfamyl; or a pharmaceutically-acceptable salt thereof.

- 5 A preferred class of compounds consists of those compounds of Formula IV wherein R³ is selected from lower alkyl, lower haloalkyl, lower aralkoxyalkyl, lower aryloxyalkyl, lower alkoxycarbonyl, lower arylthioalkyl, lower heteroaralkylthioalkyl, lower heteroarylthioalkyl,
10 lower N-aryl-N-alkylaminoalkyl, lower heteroarylalkoxyalkyl and aryl selected from naphthyl, phenyl and biphenyl, wherein the aryl radical is optionally substituted at a substitutable position with halo, lower alkoxy and lower haloalkoxy; and wherein R¹¹
15 and R¹² are independently selected from hydrido, halo, lower alkyl, lower haloalkyl, lower alkoxy, lower alkylsulfonyl, lower haloalkylsulfonyl and sulfamyl; or a pharmaceutically-acceptable salt thereof.

- A class of compounds of particular interest
20 consists of those compounds of Formula IV wherein R³ is selected from methyl, ethyl, isopropyl, tert-butyl, isobutyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl,
25 difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, ethoxycarbonyl, methoxycarbonyl, benzyloxymethyl, phenylthiomethyl, pyridylthiomethyl, pyridylmethylthiomethyl, phenyloxymethyl, 4-
30 chlorophenyloxymethyl, N-phenyl-N-methylaminomethyl, quinolyloxymethyl and aryl selected from naphthyl and phenyl, wherein the aryl radical is optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methoxy, ethoxy, isopropoxy, tert-
35 butoxy, propoxy, butoxy, isobutoxy, pentoxy, methylenedioxy and trifluoromethoxy; and wherein R¹¹ and R¹² are independently selected from hydrido, fluoro,

chloro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, 5 difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, methoxy, ethoxy, isopropoxy, *tert*-butoxy, propoxy, butoxy, isobutoxy, pentoxy, methylenedioxy, methylsulfonyl, fluoromethylsulfonyl and 10 sulfamyl; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula IV consists of compounds and pharmaceutically-acceptable salts thereof as follows:

- 15 2-[4-(dimethylamino)-3-fluorophenyl]-4,5-dihydro-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
2-(4-chlorophenyl)-4-trifluoromethyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-
20 imidazole;
2-(4-chlorophenyl)-4-difluoromethyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
2-(4-chlorophenyl)-4-methyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-
25 imidazole;
2-(4-chlorophenyl)-4-ethyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
2-(4-chlorophenyl)-4-phenyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-
30 imidazole;
2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
35 2-(4-chlorophenyl)-4-(4-bromophenyl)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;

- 2-(4-chlorophenyl)-4-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 5 2-(4-chlorophenyl)-4-(2-naphthyl)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-(4-chlorophenyl)-4-[4-(trifluoromethoxy)phenyl]-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 10 2-(4-chlorophenyl)-4-(3-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-(4-chlorophenyl)-4-(3-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 15 2-(4-chlorophenyl)-4-(4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-(4-chlorophenyl)-4-phenoxyethyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 20 2-(4-chlorophenyl)-4-(4-chlorophenoxy)methyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 25 2-(4-chlorophenyl)-4-(4-fluorophenoxy)methyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-(4-chlorophenyl)-4-phenylthiomethyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 30 2-(4-chlorophenyl)-4-(N-phenyl-N-methylamino)methyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 35 2-(4-chlorophenyl)-4-(2-quinolyl)methoxymethyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;

- 2-(4-chlorophenyl)-4-methoxymethyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 5 2-(4-chlorophenyl)-4-(4-methoxybenzyloxy)methyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-(4-chlorophenyl)-4-hydroxymethyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 10 2-(4-chlorophenyl)-4-formyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-(4-chlorophenyl)-4-cyano-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 15 2-(4-chlorophenyl)-4-benzyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-(4-chlorophenyl)-4-phenylethyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 20 2-(4-chlorophenyl)-4-hexyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-(4-chlorophenyl)-4-hexylcarbonyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 25 2-(4-chlorophenyl)-4-phenylcarbonyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-(4-chlorophenyl)-4-benzylcarbonyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 30 2-(4-chlorophenyl)-4-(1-hydroxy-1-phenyl-methyl)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 35 2-(4-chlorophenyl)-4-(1-hexanol)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;

- 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-(4-chlorophenyl)-4-octyl-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 5 2-(4-chlorophenyl)-4-methoxy-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-(4-chlorophenyl)-4-butoxy-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 10 2-(4-chlorophenyl)-4-methylthio-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-(4-chlorophenyl)-4-(2-thienyl)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 15 2-(4-chlorophenyl)-4-(2-furyl)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 20 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(4-pyridyl)-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-(4-chlorophenyl)-4-chloro-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 25 2-(4-chlorophenyl)-4-fluoro-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- [2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxylic acid;
- 30 methyl[2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxylate;
- [2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxamide;
- methyl[2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxamide;
- 35 4-[2-(4-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;

- 4-[2-(4-chlorophenyl)-4-difluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-methyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 5 4-[2-(4-chlorophenyl)-4-ethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-phenyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-(4-fluorophenyl)-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 10 4-[2-(4-chlorophenyl)-4-(4-bromophenyl)-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-(4-chlorophenyl)-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 15 4-[2-(4-chlorophenyl)-4-(2-naphthyl)-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-[4-(trifluoromethoxy)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 20 4-[2-(4-chlorophenyl)-4-(3-chlorophenyl)-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-(3-fluorophenyl)-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-(4-methoxyphenyl)-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 25 4-[2-(4-chlorophenyl)-4-phenoxyethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-(4-chlorophenoxy)methyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 30 4-[2-(4-chlorophenyl)-4-(4-fluorophenoxy)methyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-phenylthiomethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 35

- 4-[2-(4-chlorophenyl)-4-(N-phenyl-N-methylamino)methyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 5 4-[2-(4-chlorophenyl)-4-(2-quinolyl)methoxymethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-methoxymethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 10 4-[2-(4-chlorophenyl)-4-(4-methoxybenzyloxy)methyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-hydroxymethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 15 4-[2-(4-chlorophenyl)-4-formyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-cyano-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-benzyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 20 4-[2-(4-chlorophenyl)-4-phenylethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-hexyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 25 4-[2-(4-chlorophenyl)-4-hexylcarbonyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-phenylcarbonyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-benzylcarbonyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 30 4-[2-(4-chlorophenyl)-4-(1-hydroxy-1-phenyl-methyl)-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-(1-hexanol)-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 35 4-[2-(4-chlorophenyl)-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;

- 4-[2-(4-chlorophenyl)-4-octyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-methoxy-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 5 4-[2-(4-chlorophenyl)-4-butoxy-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-methylthio-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-(3-thienyl)-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 10 4-[2-(4-chlorophenyl)-4-(2-furyl)-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-(4-pyridyl)-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 15 4-[2-(4-chlorophenyl)-4-chloro-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)-4-fluoro-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- [2-(4-chlorophenyl)-1-[4-(aminosulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxylic acid;
- 20 methyl[2-(4-chlorophenyl)-1-[4-(aminosulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxylate;
- [2-(4-chlorophenyl)-1-[4-(aminosulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxamide;
- 25 methyl[2-(4-chlorophenyl)-1-[4-(aminosulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxamide;
- 2-[4-(methylsulfonyl)phenyl]-1-(4-methylphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(3-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 30 1-[4-(methylsulfonyl)phenyl]-2-(4-methyl-3-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 5-[1-[4-(methylsulfonyl)phenyl]-4-hydroxy-4-trifluoromethyl-4,5-dihydro-1H-imidazol-2-yl]-1,3-benzodioxole;
- 35

- 1-[4-(methylsulfonyl)phenyl]-2-(4-methoxyphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-(3-fluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 5 1-[4-(methylsulfonyl)phenyl]-2-(4-fluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-(4-methoxy-3-fluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 10 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 15 1-[4-(methylsulfonyl)phenyl]-2-[4-(trifluoromethyl)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-(4-bromophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 20 1-[4-(methylsulfonyl)phenyl]-2-(4-ethylphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-(4-butylphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-[4-(difluoromethyl)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 25 1-[4-(methylsulfonyl)phenyl]-2-(4-butoxyphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-[4-(methylthio)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 30 1-[4-(methylsulfonyl)phenyl]-2-(4-methoxy-3,5-dichlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-(4-methyl-3,5-difluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 35

- 1-[4-(methylsulfonyl)phenyl]-2-(2,4-dichlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
1-[4-(methylsulfonyl)phenyl]-2-(3,4-dichlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
5 1-[4-(methylsulfonyl)phenyl]-2-[4-(trifluoromethyl)phenyl]-4-trifluoromethoxy-4-hydroxy-4,5-dihydro-1H-imidazole;
2-(3,5-dimethyl-4-methoxy-phenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-4-hydroxy-
10 4,5-dihydro-1H-imidazole;
2-(3,4-dimethylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
2-(4-aminophenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
15 4-[2-(4-methylphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(3-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-methyl-3-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
20 5-[1-[4-(aminosulfonyl)phenyl]-4-hydroxy-4-trifluoromethyl-4,5-dihydro-1H-imidazol-2-yl]-1,3-benzodioxole;
25 4-[2-(4-methoxyphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(3-fluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-fluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
30 4-[2-(4-methoxy-3-fluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-phenyl-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
35

- 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 5 4-[2-[4-(trifluoromethyl)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 10 4-[2-(4-bromophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(2-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-ethylphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-butylphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 15 4-[2-[4-(difluoromethyl)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-butoxyphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 20 4-[2-[4-(methylthio)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-methoxy-3,5-dichloro-phenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 25 4-[2-(4-methyl-3,5-difluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(2,4-dichlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 30 4-[2-(3,4-dichlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-[4-(trifluoromethoxy)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 35 4-[2-(3,5-dimethyl-4-methoxy-phenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;

- 4-[2-(3,4-dimethylphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-aminophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide;
- 5 1-(4-chlorophenyl)-4-trifluoromethyl-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-(4-chlorophenyl)-4-difluoromethyl-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 10 1-(4-chlorophenyl)-4-methyl-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-(4-chlorophenyl)-4-ethyl-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 15 1-(4-chlorophenyl)-4-phenyl-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-(4-chlorophenyl)-4-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 20 4-(4-bromophenyl)-1-(4-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 25 1-(4-chlorophenyl)-4-(3-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-(4-chlorophenyl)-4-(3-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 30 1-(4-chlorophenyl)-4-(4-methoxyphenyl)-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1,4-bis(4-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 35

- 1-(4-chlorophenyl)-4-(2-naphthyl)-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 5 1-(4-chlorophenyl)-4-[4-(trifluoromethoxy)phenyl]-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-(4-chlorophenyl)-4-phenoxyethyl-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 10 1-(4-chlorophenyl)-4-(4-chlorophenoxy)methyl-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-(4-chlorophenyl)-4-(4-fluorophenoxy)methyl-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 15 1-(4-chlorophenyl)-4-phenylthiomethyl-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-(4-chlorophenyl)-4-(N-phenyl-N-methylamino)methyl-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 20 1-(4-chlorophenyl)-4-(2-quinolyl)methoxymethyl-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 25 1-(4-chlorophenyl)-4-methoxymethyl-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-(4-chlorophenyl)-4-(4-methoxybenzyloxy)methyl-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 30 1-(4-chlorophenyl)-4-hydroxymethyl-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-(4-chlorophenyl)-4-formyl-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 35

- 1-(4-chlorophenyl)-4-cyano-2-[4-(methylsulfonyl)phenyl]-
4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-(4-chlorophenyl)-4-benzyl-2-[4-
(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-
5 imidazole;
- 1-(4-chlorophenyl)-4-phenylethyl-2-[4-
(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-
imidazole;
- 1-(4-chlorophenyl)-4-hexyl-2-[4-(methylsulfonyl)phenyl]-
10 4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-(4-chlorophenyl)-4-hexylcarbonyl-2-[4-
(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-
imidazole;
- 1-(4-chlorophenyl)-4-phenylcarbonyl-2-[4-
15 (methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-
imidazole;
- 1-(4-chlorophenyl)-4-benzylcarbonyl-2-[4-
(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-
imidazole;
- 20 1-(4-chlorophenyl)-4-(1-hydroxy-2-phenyl-methyl)-2-[4-
(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-
imidazole;
- 1-(4-chlorophenyl)-4-(1-hexanol)-2-[4-
(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-
25 imidazole;
- 1-(4-chlorophenyl)-2-[(methylsulfonyl)phenyl]-4-hydroxy-
4,5-dihydro-1H-imidazole;
- 1-(4-chlorophenyl)-4-octyl-2-[4-(methylsulfonyl)phenyl]-
4-hydroxy-4,5-dihydro-1H-imidazole;
- 30 1-(4-chlorophenyl)-4-methoxy-2-[4-
(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-
imidazole;
- 1-(4-chlorophenyl)-4-butoxy-2-[4-
(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-
35 imidazole;

- 1-(4-chlorophenyl)-4-methylthio-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 5 1-(4-chlorophenyl)-4-(2-thienyl)-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-(4-chlorophenyl)-4-(2-furyl)-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 10 1-(4-chlorophenyl)-4-(4-pyridyl)-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 1-(4-chlorophenyl)-4-chloro-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- 15 1-(4-chlorophenyl)-4-fluoro-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazole;
- [1-(4-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxylic acid;
- 20 methyl[1-(4-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxylate;
- [1-(4-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxamide;
- 25 methyl[1-(4-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxamide;
- 4-[1-(4-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-difluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 30 4-[1-(4-chlorophenyl)-4-methyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-ethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 35 4-[1-(4-chlorophenyl)-4-phenyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;

- 4-[1-(4-chlorophenyl)-4-(4-fluorophenyl)-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-(4-bromophenyl)-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 5 4-[1-(4-chlorophenyl)-4-(4-chlorophenyl)-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-(2-naphthyl)-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-[4-(trifluoromethoxy)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 10 4-[1-(4-chlorophenyl)-4-(3-chlorophenyl)-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-(3-fluorophenyl)-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 15 4-[1-(4-chlorophenyl)-4-(4-methoxyphenyl)-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-phenoxyethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 20 4-[1-(4-chlorophenyl)-4-(4-chlorophenoxy)methyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-(4-fluorophenoxy)methyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 25 4-[1-(4-chlorophenyl)-4-phenylthiomethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-(N-phenyl-N-methylamino)methyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 30 4-[1-(4-chlorophenyl)-4-(2-quinolyl)methoxymethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-methoxymethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 35

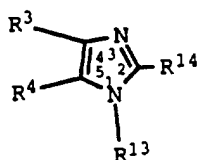
- 4-[1-(4-chlorophenyl)-4-(4-methoxybenzyloxy)methyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 5 4-[1-(4-chlorophenyl)-4-hydroxymethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-formyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-cyano-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 10 4-[1-(4-chlorophenyl)-4-benzyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-phenylethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-hexyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 15 4-[1-(4-chlorophenyl)-4-hexylcarbonyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-phenylcarbonyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 20 4-[1-(4-chlorophenyl)-4-benzylcarbonyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-(1-hydroxy-2-phenyl-methyl)-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 25 4-[1-(4-chlorophenyl)-4-(1-hexanol)-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-octyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 30 4-[1-(4-chlorophenyl)-4-methoxy-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-butoxy-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 35 4-[1-(4-chlorophenyl)-4-methylthio-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;

- 4-[1-(4-chlorophenyl)-4-(2-thienyl)-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-(2-furyl)-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
5 4-[1-(4-chlorophenyl)-4-(3-pyridyl)-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-chloro-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-fluoro-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
10 [1-(4-chlorophenyl)-2-[4-(aminosulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxylic acid;
methyl[1-(4-chlorophenyl)-2-[4-(aminosulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxylate;
15 [1-(4-chlorophenyl)-2-[4-(aminosulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxamide;
methyl[1-(4-chlorophenyl)-2-[4-(aminosulfonyl)phenyl]-4-hydroxy-4,5-dihydro-1H-imidazol-4-yl]carboxamide;
2-[4-(methylsulfonyl)phenyl]-1-(4-methylphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
20 2-[4-(methylsulfonyl)phenyl]-1-(3-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
2-[4-(methylsulfonyl)phenyl]-1-(4-methyl-3-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
25 5-[2-[4-(methylsulfonyl)phenyl]-4-hydroxy-4-trifluoromethyl-4,5-dihydro-1H-imidazol-1-yl]-1,3-benzodioxole;
2-[4-(methylsulfonyl)phenyl]-1-(4-methoxyphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
30 2-[4-(methylsulfonyl)phenyl]-1-(3-fluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
2-[4-(methylsulfonyl)phenyl]-1-(4-fluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
35 2-[4-(methylsulfonyl)phenyl]-1-(4-methoxy-3-fluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;

- 2-[4-(methylsulfonyl)phenyl]-1-phenyl-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 5 2-[4-(methylsulfonyl)phenyl]-1-[4-(trifluoromethyl)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(4-bromophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 10 2-[4-(methylsulfonyl)phenyl]-1-(1-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(4-ethylphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 15 2-[4-(methylsulfonyl)phenyl]-1-(4-butylphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-[4-(difluoromethyl)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 20 2-[4-(methylsulfonyl)phenyl]-1-(4-butoxyphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-[4-(methylthio)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(4-methoxy-3,5-dichlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 25 2-[4-(methylsulfonyl)phenyl]-1-(4-methyl-3,5-difluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 30 2-[4-(methylsulfonyl)phenyl]-1-(2,4-dichlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(3,4-dichlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-[4-(trifluoromethyl)phenyl]-4-trifluoromethoxy-4-hydroxy-4,5-dihydro-1H-imidazole;
- 35

- 2-[4-(methylsulfonyl)phenyl]-1-(3,5-dimethyl-4-methoxy-phenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-[4-(methylsulfonyl)phenyl]-1-(3,4-dimethylphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 5 2-[4-(methylsulfonyl)phenyl]-1-(4-aminophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazole;
- 2-[1-(4-methylphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 10 4-[1-(3-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-methyl-3-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 15 5-[2-[4-(aminosulfonyl)phenyl]-4-hydroxy-4,5-dihydro-4-trifluoromethyl-1H-imidazol-1-yl]-1,3-benzodioxole;
- 4-[1-(3-fluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(4-fluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 20 4-[1-(4-methoxy-3-fluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-phenyl-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 25 4-[1-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-[4-(trifluoromethyl)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 30 4-[1-(4-bromophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 4-[1-(1-chlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
- 35 4-[1-(4-ethylphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;

- 4-[1-(4-butylphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
 4-[1-[4-(difluoromethyl)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
 5 4-[1-(4-butoxyphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
 4-[1-[4-(methylthio)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
 10 4-[1-(4-methoxy-3,5-dichloro-phenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
 4-[1-(4-methyl-3,5-difluorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
 15 4-[1-(2,4-dichlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
 4-[1-(3,4-dichlorophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
 20 4-[1-[4-(trifluoromethoxy)phenyl]-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
 4-[1-(3,5-dimethyl-4-methoxy-phenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide;
 25 4-[1-(3,4-dimethylphenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide; and
 4-[1-(4-aminophenyl)-4-trifluoromethyl-4-hydroxy-4,5-dihydro-1H-imidazol-2-yl]benzenesulfonamide.
 30 Within Formula I there is a fourth subclass of compounds of high interest represented by Formula V:



(V)

wherein R^3 is a radical selected from hydrido, alkyl, haloalkyl, aralkyl, heterocycloalkyl, heteroaralkyl, acyl, cyano, alkoxy, alkylthio, alkylthioalkyl, alkylsulfonyl, cycloalkylthio, cycloalkylthioalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, haloalkylsulfonyl, arylsulfonyl, halo, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocyclocarbonyl, cyanoalkyl, aminoalkyl, alkylaminoalkyl, N-arylaminalkyl, N-alkyl-N-arylaminalkyl, carboxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, haloalkylcarbonyl, carboxyl, aminocarbonyl, alkylaminocarbonyl, alkylaminocarbonylalkyl, heteroarylalkoxyalkyl, heteroaryloxyalkyl, heteroarylthioalkyl, aralkoxy, aralkylthio, heteroaralkoxy, heteroaralkylthio, heteroarylalkylthioalkyl, heteroaryloxy, heteroarylthio, arylthioalkyl, aryloxyalkyl, arylthio, aryloxy, aralkylthioalkyl, aralkoxyalkyl, aryl and heteroaryl; wherein R^4 is a radical selected from hydrido, alkyl and halo; and wherein R^{13} and R^{14} are independently selected from aryl and heterocyclo, wherein R^{13} and R^{14} are optionally substituted at a substitutable position with one or more radicals independently selected from alkylsulfonyl, aminosulfonyl, halo, alkylthio, alkyl, cyano, carboxyl, alkoxycarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, alkoxyalkyl, haloalkoxy, amino, alkylamino, arylamino and nitro; provided at least one of R^{13} and R^{14} is aryl substituted with alkylsulfonyl or aminosulfonyl; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds consists of those compounds of Formula V wherein R^3 is a radical selected from hydrido, lower alkyl, lower haloalkyl, lower aralkyl, lower heterocycloalkyl, lower heteroaralkyl, acyl, cyano, lower alkoxy, lower alkylthio, lower

alkylsulfonyl, phenylsulfonyl, lower haloalkylsulfonyl, halo, lower hydroxyalkyl, lower alkoxyalkyl, lower alkylcarbonyl, lower haloalkylcarbonyl, phenylcarbonyl, lower aralkylcarbonyl, lower cyanoalkyl, lower aminoalkyl, lower alkylaminoalkyl, lower N-arylaminoalkyl, lower N-alkyl-N-arylaminoalkyl, lower carboxyalkyl, lower alkoxycarbonylalkyl, lower alkoxycarbonyl, carboxyl, lower alkylthioalkyl, aminocarbonyl, lower alkylaminocarbonyl, lower alkylaminocarbonylalkyl, lower aralkoxy, lower aralkylthio, lower heteroaralkoxy, lower heteroaralkylthio, lower heteroarylalkoxyalkyl, lower heteroarylalkylthioalkyl, lower heteroaryloxyalkyl, lower heteroarylthioalkyl, lower heteroaryloxy, lower heteroarylthio, lower arylthioalkyl, lower aryloxyalkyl, lower arylthio, lower aryloxy, lower aralkylthioalkyl, lower aralkoxyalkyl, aryl selected from phenyl and naphthyl, 5 or 6 membered heteroaryl, wherein the aryl and heteroaryl radicals are optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, cyano, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl and lower haloalkoxy; wherein R^4 is a radical selected from hydrido, lower alkyl and halo; and wherein R^{13} and R^{14} are independently selected from phenyl and heteroaryl, wherein R^{13} and R^{14} are optionally substituted at a substitutable position with one or more radicals independently selected from lower methylsulfonyl, aminosulfonyl, lower alkylthio, lower alkyl, lower haloalkyl, lower alkoxy, lower hydroxyalkyl, lower alkoxyalkyl, and lower haloalkoxy; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula V wherein R^3 is a radical selected from hydrido, methyl, ethyl, isopropyl, tert-butyl, isobutyl, pentyl, hexyl,

- fluoromethyl, difluoromethyl, trifluoromethyl,
chloromethyl, dichloromethyl, trichloromethyl,
pentafluoroethyl, heptafluoropropyl,
difluorochloromethyl, dichlorofluoromethyl,
5 difluoroethyl, difluoropropyl, dichloroethyl,
dichloropropyl, benzyl, phenylethyl, phenylpropyl,
furylmethyl, morpholinomethyl, pyrrolidinylmethyl,
piperazinylmethyl, piperidinylmethyl, pyridylmethyl,
thienylmethyl, formyl, cyano, methoxy, ethoxy, propoxy,
10 n-butoxy, methylthio, ethylthio, isopropylthio,
methylsulfonyl, phenylsulfonyl,
trifluoromethylsulfonyl, fluoro, chloro, bromo,
hydroxymethyl, hydroxyethyl, methoxymethyl,
ethoxymethyl, methylthiomethyl, isopropylthiomethyl,
15 cyclohexylthiomethyl, benzyloxy, benzylthio,
methylcarbonyl, ethylcarbonyl, phenylcarbonyl,
trifluoromethylcarbonyl, difluoromethylcarbonyl,
fluoromethylcarbonyl, benzylcarbonyl,
pyrrolidinylcarbonyl, cyanomethyl, cyanobutyl,
20 aminomethyl, methylaminomethyl, N-phenylaminomethyl, N-
methyl-N-phenylaminomethyl, acetyl, propanoyl,
butanoyl, methoxycarbonylmethyl, ethoxycarbonylethyl,
methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl,
tert-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl,
25 isobutoxycarbonyl, pentoxycarbonyl, carboxyl,
carboxymethyl, carboxypropyl, aminocarbonyl,
methylaminocarbonyl, N,N-diethylaminocarbonyl, N-
methoxy-N-methylaminocarbonyl,
methylaminocarbonylmethyl, pyridyloxy, pyridylthio,
30 phenyloxy, 4-chlorophenoxy, furylmethoxy,
furylmethylthio, thienylmethoxy, quinolylmethoxy,
pyridylmethoxy, 5-phenylpyridyl-2-methoxy,
thienylmethylthio, pyridylmethylthio,
quinolylmethoxymethyl, furylbutoxyethyl,
35 pyridyloxymethyl, pyridylmethoxymethyl,
thienyloxyhexyl, thienylthiomethyl, pyridylthiohexyl,
furyloxymethyl, furylmethylthiomethyl,

quinolylmethylthioethyl, phenylthiomethyl, 2-chlorophenylthiomethyl, 2,6-dichlorophenylthiomethyl, 4-methylphenylthiomethyl, 2-isopropylphenylthiomethyl, 2-methylphenylthiomethyl, phenyloxymethyl, 4-chlorophenyloxymethyl, 4-methylphenyloxymethyl, benzyloxymethyl, 4-methoxybenzyloxymethyl, naphthyl, phenyl, thienyl, furyl, pyridyl, wherein the thienyl, furyl, pyridyl and phenyl radicals are optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methylsulfinyl, methyl, ethyl, isopropyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, hydroxymethyl, hydroxyethyl and trifluoromethoxy; wherein R^4 is a radical selected from hydrido, methyl, ethyl, fluoro, chloro and bromo; and wherein R^{13} and R^{14} is selected from phenyl, imidazolyl, thienyl, thiazolyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazinyl, pyrimidinyl, quiolinyl, indolylbenzimidazolyl, pyrazolyl and pyridyl, wherein R^{13} and R^{14} are optionally substituted at a substitutable position with one or more radicals independently selected from methylsulfonyl, aminosulfonyl, fluoromethylsulfonyl, difluoromethylsulfonyl, fluoro, chloro, bromo, methylthio, methylsulfinyl, methyl, ethyl, isopropyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl,

heptafluoropropyl, difluorochloromethyl,
dichlorofluoromethyl, difluoroethyl, difluoropropyl,
dichloroethyl, dichloropropyl, hydroxyl, methoxy,
methylenedioxy, ethoxy, propoxy, n-butoxy,
5 hydroxymethyl, hydroxyethyl, methoxymethyl,
ethoxymethyl, trifluoromethoxy, amino, methylamino,
N,N-diethylamino, phenylamino and nitro; or a
pharmaceutically-acceptable salt thereof.

A class of compounds of even more particular
10 interest consists of those compounds of Formula V
wherein R^3 is a radical selected from hydrido, methyl,
ethyl, isopropyl, tert-butyl, isobutyl, pentyl, hexyl,
fluoromethyl, difluoromethyl, trifluoromethyl,
chloromethyl, dichloromethyl, trichloromethyl,
15 pentafluoroethyl, heptafluoropropyl,
difluorochloromethyl, dichlorofluoromethyl,
difluoroethyl, difluoropropyl, dichloroethyl, and
dichloropropyl; wherein R^4 is hydrido; wherein R^{13} is
phenyl optionally substituted with methylsulfonyl or
20 aminosulfonyl; and wherein R^{14} is selected from
imidazolyl, thienyl, thiazolyl, pyrrolyl, oxazolyl,
isoxazolyl, triazolyl, pyrimidinyl, quiolinyl, indolyl,
benzimidazolyl, pyrazolyl and pyridyl, wherein R^{14} is
optionally substituted at a substitutable position with
25 one or more radicals independently selected from
methylthio, methyl, ethyl, isopropyl, tert-butyl,
isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl,
trifluoromethyl, chloromethyl, dichloromethyl,
trichloromethyl, pentafluoroethyl, heptafluoropropyl,
30 difluorochloromethyl, dichlorofluoromethyl,
difluoroethyl, difluoropropyl, dichloroethyl,
dichloropropyl, methoxy, methylenedioxy, ethoxy,
propoxy, n-butoxy, hydroxymethyl, hydroxyethyl,
methoxymethyl, ethoxymethyl, and trifluoromethoxy; or a
35 pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula V consists of compounds and pharmaceutically-acceptable salts thereof as follows:

- 5 1-methyl-3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]-1H-indole;
4-[2-(1-methylindol-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(isoquinol-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
10 4-[2-(2-methyloxazol-4-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(2-methylthiazol-4-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
15 4-[2-(oxazol-4-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(1-methylpyrazol-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(5-methylisoxazol-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
20 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]thiophene;
25 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]thiophene;
4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
2-methyl-3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
30 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(pyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
35 3-fluoro-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

- 3-chloro-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
4-[2-(5-fluoropyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
5 4-[2-(5-chloropyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
5-methyl-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
4-methyl-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
10 2-methoxy-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
5-methoxy-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
15 4-methoxy-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
2-chloro-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
5-chloro-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
20 4-chloro-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
2-fluoro-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
25 4-fluoro-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
4-fluoro-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
4-[2-(5-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
30 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(6-methoxypyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
35 4-[2-(5-methoxypyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

- 4-[2-(4-methoxypyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(6-chloropyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
5 4-[2-(5-chloropyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-chloropyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(6-fluoropyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
10 4-[2-(5-fluoropyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(4-fluoropyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
15 3-methoxy-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
3-[4-methyl-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine 1-oxide;
20 3-[4-[4-(fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazol-2-yl]pyridine;
5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-(methylthio)pyridine;
25 3-[4-(difluoromethyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazol-2-yl]pyridine;
4-[2-(5-methoxypyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[4-methyl-2-(3-pyridinyl)-1H-imidazol-1-yl]benzenesulfonamide;
30 4-[2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide 1-oxide;
4-[4-(4-fluorophenyl)-2-(3-pyridinyl)-1H-imidazol-1-yl]benzenesulfonamide;
35 4-[2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide 1-oxide;

- 4-[4-(4-fluorophenyl)-2-(3-pyridinyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-[6-(methylthio)pyridin-3-yl]-4-trifluoromethyl]-1H-imidazol-1-yl]benzenesulfonamide;
- 5 4-[4-(difluoromethyl)-2-(3-pyridinyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 10 2-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 15 2-methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 1-methyl-3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridinium iodide;
- 20 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine 1-oxide;
- 3-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 25 2-methoxy-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 2-[4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 3-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine 1-oxide;
- 30 3-methoxy-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 4-[2-(3-methoxypyridin-5-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 35 2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]quinoline;

2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyrazine;
2-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]thiazole; and
5 4-[2-(5-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide.

Compounds of Formula V, especially where R¹⁴ is pyridyl, may form N-oxides, which may be active forms or
10 prodrugs which would be converted to compounds of Formula V *in vivo*.

Compounds of Formula V would also be capable of inhibiting cytokines, such as TNF, IL-1, IL-6, and IL-8. As such, the compounds can be used in the manufacture of
15 a medicament or in a method for the treatment for the prophylactic or therapeutic treatment of diseases mediated by cytokines, such as TNF, IL-1, IL-6, and IL-8.

The term "hydrido" denotes a single hydrogen atom
20 (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH₂-) radical. Where used, either alone or within other terms such as "haloalkyl",
25 "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten
30 carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. The term "halo" means halogens
35 such as fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as

defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxyalkyl radicals are "lower alkoxyalkyl" radicals having one to six carbon atoms and one or two alkoxy radicals. Examples of such radicals include methoxymethyl, methoxyethyl, ethoxyethyl, methoxybutyl and methoxypropyl. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more

halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" or haloalkoxyalkyl radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "cyanoalkyl" embraces radicals having a cyano or nitrile (-CN) radical attached to an alkyl radicals as described above. More preferred cyanoalkyl radicals are "lower cyanoalkyl" radicals having one to six carbon atoms. Examples of such lower cyanoalkyl radicals include cyanomethyl, cyanopropyl, cyanoethyl and cyanobutyl. The term "cycloalkyl" embraces saturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "cycloalkenyl" embraces unsaturated cyclic radicals having three to ten carbon atoms. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having about five to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Such aryl radicals may be substituted at a substitutable position with one or more substituents selected from halo, alkylthio, alkylsulfinyl, alkyl, cyano, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl and haloalkoxy. The terms "heterocyclic" and "heterocyclo" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the

heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, 5 imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms 10 and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of 15 unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 20 pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, 25 isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for 30 example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen 35 atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed

heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclic group" may be substituted at a substitutable position with one or more substituents selected from halo, alkylthio, alkylsulfinyl, alkyl, cyano, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl and haloalkoxy. More preferred heteroaryl radicals include five to six membered heteroaryl radicals. The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals. More preferred heterocycloalkyl radicals are "lower heterocycloalkyl" radicals having one to six carbon atoms and a heterocyclic radical. Examples include such radicals as pyrrolidinylmethyl. The term "heteroarylalkyl" embraces heteroaryl-substituted alkyl radicals. More preferred heteroarylalkyl radicals are "lower heteroarylalkyl" radicals having one to six carbon atoms and a heteroaryl radical. Examples include such heteroarylalkyl radicals such as pyridylmethyl and thienylmethyl. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term

"alkylthioalkyl" embraces alkylthio radicals attached to an alkyl radical. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms and an alkylthio radical as described above. Examples of such radicals include methylthiomethyl. The term "arylthio" embraces radicals containing an aryl radical, attached to a divalent sulfur atom, such as a phenylthio radical. The term "arylthioalkyl" embraces arylthio radicals attached to an alkyl radical. More preferred arylthioalkyl radicals are "lower arylthioalkyl" radicals having alkyl radicals of one to six carbon atoms and an arylthio radical as described above. Examples of such radicals include phenylthiomethyl. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent $-S(=O)-$ radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkylsulfonyl" radicals. More preferred haloalkylsulfonyl radicals are "lower haloalkylsulfonyl" radicals having one or more halo atoms attached to lower alkylsulfonyl radicals as described above. Examples of such lower haloalkylsulfonyl radicals include

fluoromethylsulfonyl, trifluoromethylsulfonyl and chloromethylsulfonyl. The term "arylsulfonyl" embraces aryl radicals as defined above, attached to a sulfonyl radical. Examples of such radicals include

5 phenylsulfonyl. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denotes $\text{NH}_2\text{O}_2\text{S}-$. The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include formyl, alkanoyl and aroyl radicals.

10 The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-\text{CO}_2\text{H}$. The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes $-(\text{C}=\text{O})-$. The term "alkoxycarbonyl" means a radical containing an

15 alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Preferably, "lower alkoxy carbonyl" embraces alkoxy radicals having one to six carbon atoms. Examples of such "lower alkoxy carbonyl" ester radicals include substituted or

20 unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl

25 radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. The aryl in said aralkyl may be substituted at a substitutable position with one or more substituents

30 selected from halo, alkylthio, alkylsulfinyl, alkyl, cyano, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable. The terms "alkylcarbonyl", "arylcabonyl" and "aralkylcarbonyl" include radicals

35 having alkyl, aryl and aralkyl radicals, respectively, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred alkylcarbonyl radicals

are "lower alkylcarbonyl" radicals having one to six carbon atoms. Examples of such radicals include methylcarbonyl and ethylcarbonyl. More preferred aralkylcarbonyl radicals are "lower aralkylcarbonyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such aralkylcarbonyl radicals include benzylcarbonyl. An example of an arylcarbonyl radical is phenylcarbonyl. The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. More preferred alkoxycarbonylalkyl radicals are "lower alkoxycarbonylalkyl" having lower alkoxycarbonyl radicals as defined above attached to one to six carbon atoms. Examples of such lower alkoxycarbonylalkyl radicals include methoxycarbonylmethyl. The term "haloalkylcarbonyl" embraces radicals having a haloalkyl radical as described above attached to a carbonyl radical. More preferred radicals are "lower haloalkylcarbonyl" radicals where lower haloalkyl radicals, as described above are attached to a carbonyl radical. The term "carboxyalkyl" embraces radicals having a carboxy radical as defined above, attached to an alkyl radical. The alkanoyl radicals may be substituted or unsubstituted, such as formyl, acetyl, propanoyl, butanoyl, isobutanoyl, valeryl, isovaleryl, pivaloyl, hexanoyl or the like. The term "heteroaralkyl" embraces heteroaryl-substituted alkyl radicals. More preferred heteroaralkyl radicals are "lower heteroaralkyl" radicals having five to six membered heteroaryl radicals attached to one to six carbon atoms. Examples of such radicals include pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The term "aryloxy" embraces aryl radicals, as defined above, attached to an oxygen atom. Examples

of such radicals include phenoxy. The term "heteroaryloxy" embraces heteroaryl radicals as defined above attached to an oxygen radical. More preferred heteroaryloxy radicals are "lower heteroaryloxy" radicals having five to six membered heteroaryl radicals. The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. The term "aralkoxyalkyl" embraces alkyl radicals having one or more aralkoxy radicals attached to the alkyl radical, that is, to form monoaralkyloxyalkyl and diaralkyloxyalkyl radicals. The "aralkoxy" or "aralkoxyalkyl" radicals may be further substituted on the aryl ring portion of the radical. More preferred aralkoxyalkyl radicals are "lower aralkoxyalkyl" having an alkoxy attached to one to six carbon atoms. Examples of lower aralkoxyalkyl radicals include benzyloxymethyl. The term "cycloalkylthio" embraces radicals containing a cycloalkyl radical, of three to about ten carbon atoms attached to a divalent sulfur atom. More preferred cycloalkylthio radicals are "lower cycloalkylthio" radicals having cycloalkyl radicals of four to six carbon atoms. Examples of such lower cycloalkylthio radicals are cyclobutylthio, cyclopentylthio and cyclohexylthio. The term "cycloalkylthioalkyl" embraces radicals containing a cycloalkylthio radical, as described above, attached to an alkyl radical. More preferred cycloalkylthioalkyl radicals are "lower cycloalkylthioalkyl" radicals having cycloalkyl radicals of four to six carbon atoms and alkyl radicals of one to six carbons. The term "cycloalkylsulfonyl" embraces radicals containing a cycloalkyl radical, of three to about ten carbon atoms attached to a divalent sulfonyl radical. More preferred cycloalkylsulfonyl radicals are "lower cycloalkylsulfonyl" radicals having cycloalkyl radicals of four to six carbon atoms. Examples of such lower cycloalkylsulfonyl radicals are cyclobutylsulfonyl,

cyclopentylsulfonyl and cyclohexylsulfonyl. The term "cycloalkylsulfonylalkyl" embraces radicals containing a cycloalkylsulfonyl radical, as described above, attached to an alkyl radical. More preferred

5 cycloalkylsulfonylalkyl radicals are "lower cycloalkylsulfonylalkyl" radicals having cycloalkyl radicals of four to six carbon atoms and alkyl radicals of one to six carbons. The term "cycloalkyloxy"

10 embraces radicals containing a cycloalkyl radical, of three to about ten carbon atoms attached to a divalent oxygen atom. More preferred cycloalkyloxy radicals are "lower cycloalkyloxy" radicals having cycloalkyl radicals of four to six carbon atoms. Examples of such lower cycloalkyloxy radicals are cyclobutyloxy,

15 cyclopentyloxy and cyclohexyloxy. The term "cycloalkyloxyalkyl" embraces radicals containing a cycloalkyloxy radical, as described above, attached to an alkyl radical. More preferred cycloalkyloxyalkyl radicals are "lower cycloalkyloxyalkyl" radicals having

20 cycloalkyl radicals of four to six carbon atoms and alkyl radicals of one to six carbons. The term "heteroarylthio" embraces radicals having heteroaryl radicals attached to a sulfur radical. More preferred heteroarylthio radicals are "lower heteroarylthio"

25 radicals having five to six membered heteroaryl radicals. Examples of such radicals include 2-furylthio, 2-thienylthio, 3-thienylthio, 4-pyridylthio and 3-pyridylthio. The term "heteroarylalkylthio" denotes radicals having an heteroaryl radical attached

30 to an alkylthio radical. More preferred heteroarylalkylthio radicals are "lower heteroarylalkylthio" radicals having heteroaryl radicals attached to lower alkylthio radicals as described above. Examples of such radicals include furylmethylthio and

35 quinolylmethylthio. The term "heteroarylalkylthioalkyl" denotes radicals having an heteroaryl radical attached to an alkylthio radical further attached through the

sulfur atom to an alkyl radical. More preferred heteroarylalkylthioalkyl are "lower heteroarylalkylthioalkyl" radicals having lower heteroarylalkyl radicals as described above. Examples of such radicals include furylmethylthiomethyl and quinolylmethylthioethyl. The term "heteroarylthioalkyl" denotes radicals having an heteroaryl radical attached to a sulfur atom further attached through the sulfur atom to an alkyl radical. More preferred heteroarylthioalkyl radicals are "lower heteroarylthioalkyl" having lower heteroarylthio radicals as described above. Examples of such radicals include thienylthiomethyl and pyridylthiohexyl. The term "aralkylthio" embraces radicals having aralkyl radicals attached to a bridging sulfur atom. More preferred aralkylthio radicals are "lower aralkylthio" radicals having the aryl radicals attached to one to six carbon atoms. Examples of such radicals include benzylthio and phenylethylthio. The term "aralkylthioalkyl" embraces radicals having aralkyl radicals attached to alkyl radicals through a bridging sulfur atom. More preferred aralkylthioalkyl radicals are "lower aralkylthioalkyl" radicals having the aralkylthio radicals attached to one to six carbon atoms. Examples of such radicals include benzylthiomethyl and phenylethylthiomethyl. The term "heteroaryloxyalkyl" denotes radicals having an heteroaryl radical attached to an oxygen atom further attached through the oxygen atom to an alkyl radical. More preferred heteroaryloxyalkyl radicals are "lower heteroaryloxyalkyl" radicals having five to six membered heteroaryl radicals. Examples of such radicals include furyloxyethyl, pyridyloxymethyl and thienyloxyhexyl. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" having one to six carbon atoms. Examples include aminomethyl, aminoethyl and aminobutyl. The term "alkylaminoalkyl" embraces aminoalkyl radicals

having the nitrogen atom substituted with at least one alkyl radical. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" having one to six carbon atoms attached to a lower aminoalkyl radical as

5 described above. The term "alkylamino" denotes amino groups which have been substituted with one or two alkyl radicals. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom.

10 Suitable "alkylamino" may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "alkylaminocarbonyl" embraces alkylamino radicals, as described above, to a carbonyl radical. More preferred alkylaminocarbonyl

15 radicals are "lower alkylaminocarbonyl" having lower alkylamino radicals, as described above, attached to a carbonyl radical. Examples of such radicals include N-methylaminocarbonyl and N,N-dimethylcarbonyl. The term "arylamino" denotes amino groups which have been

20 substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The terms "N-arylaminoalkyl" and "N-aryl-N-alkylaminoalkyl" denote amino groups which have been substituted with one

25 aryl radical or one aryl and one alkyl radical, respectively, and having the aminogroup attached to an alkyl radical. More preferred arylaminoalkyl radicals are "lower arylaminoalkyl" having the arylamino radical attached to one to six carbon atoms. Examples of such

30 radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl. The term "aminocarbonyl" denotes an amide group of the formula $-C(=O)NH_2$. The term "alkylaminocarbonylalkyl" denotes an alkylaminocarbonyl group which is attached to an alkyl radical. More

35 preferred are "lower alkylaminocarbonylalkyl" having lower alkylaminocarbonyl radicals as described above attached to one to six carbon atoms. The term

"aryloxyalkyl" embraces alkyl radicals having one or more aryloxy radicals, aryl radicals attached to a divalent oxygen atom, attached to the alkyl radical, that is, to form monoaryloxyalkyl and diaryloxyalkyl radicals. The more preferred aryloxyalkyl radicals are "lower aryloxyalkyl" radicals having aryloxy radicals attached to one to six carbon atoms. Examples include phenoxymethyl. The term "heteroarylalkoxy" embraces radicals having one or more heterocyclic radicals attached to an alkoxy radical. More preferred heteroarylalkoxy radicals are "lower heteroarylalkoxy" radicals having five to six membered heteroaryl radicals. Examples of such radicals include 2-, 3-thienylmethoxy, 2-, 3-furylmethoxy and 2-, 3-, 4-pyridylmethoxy. The term "heteroarylalkoxyalkyl" embraces alkyl radicals having one or more heterocyclic radicals attached to an alkoxy radical, further attached to the alkyl radical. More preferred heteroarylalkoxyalkyl radicals are "lower heteroarylalkoxyalkyl" radicals having five to six membered heteroaryl radicals. Examples of such radicals include 2-thienylmethoxymethyl. The term "azidoalkyl" denotes alkyl radicals substituted with azido groups ($-N_3$). More preferred azidoalkyl radicals are "lower azidoalkyl" having one to six carbon atoms. Examples include azidomethyl, azidoethyl and aminopropyl.

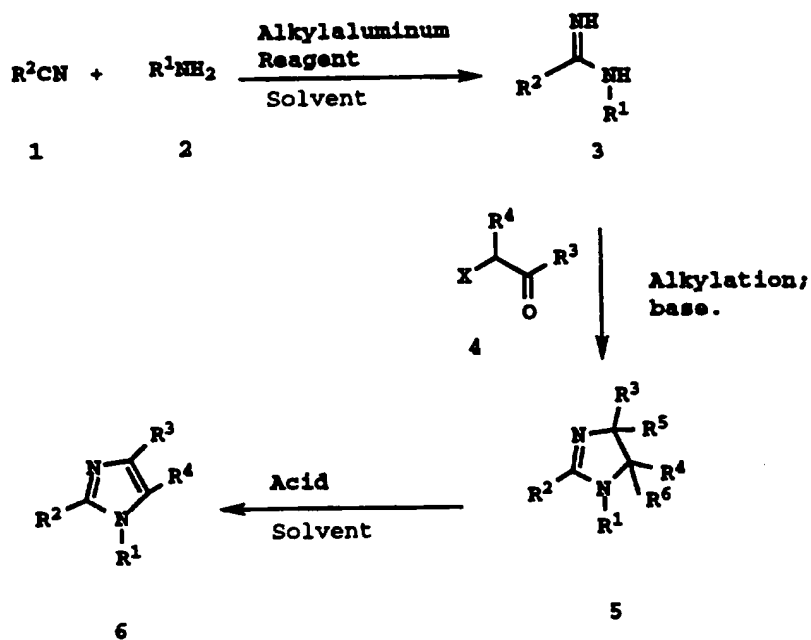
The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formula I in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of treating inflammation or inflammation-associated disorders in a subject, the method comprising administering to the subject having or susceptible to such inflammation or disorder a therapeutically-effective amount of a compound of Formula I.

Also included in the family of compounds of Formula I are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, *p*-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethylsulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, β -hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from *N,N'*-dibenzylethylenediamine, choline, chlorprocaine, diethanolamine, ethylenediamine, meglumine (*N*-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the following procedures of Schemes I-XIV, wherein the R¹-R¹⁴ substituents are as defined for Formula I-V, above, except where further noted.

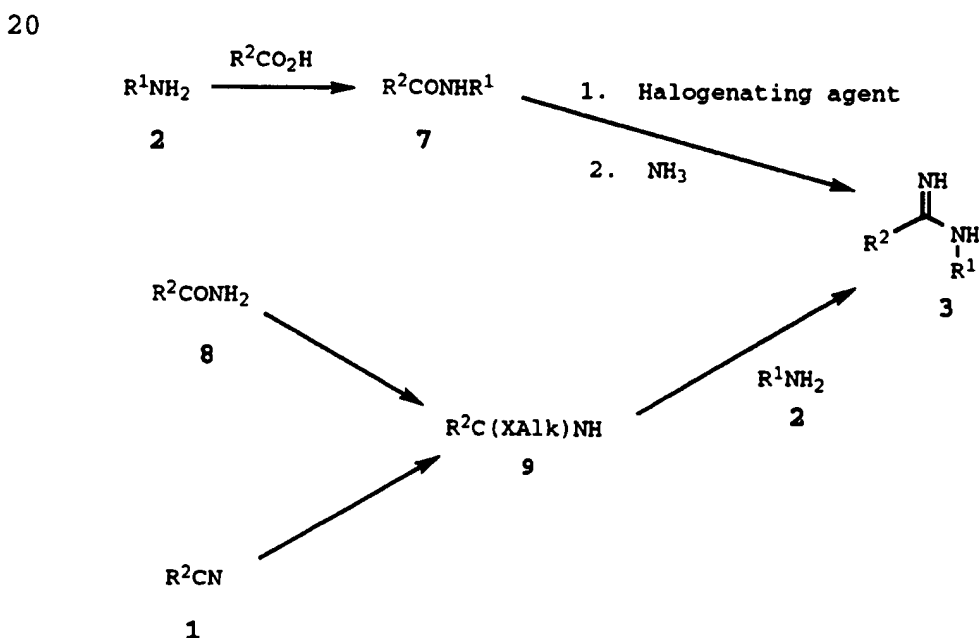
Scheme I

Scheme I shows the three step preparation of the 4,5-dihydro imidazoles 5 and substituted imidazoles 6 of the present invention. In step 1, the reaction of substituted nitriles (R²CN) 1 with primary amines (R¹NH₂) 2 in the presence of alkylaluminum reagents such as trimethylaluminum, triethylaluminum, dimethylaluminum chloride, diethylaluminum chloride in the presence of inert solvents such as toluene, benzene, and xylene, gives amidines 3. In step 2, the reaction of amidine 3 with 2-halo-ketones 4 (where X is Br or Cl) in the presence of bases, such as sodium bicarbonate, potassium carbonate, sodium carbonate, potassium bicarbonate or hindered tertiary amines such

as *N,N'*-diisopropylethylamine, gives the 4,5-dihydroimidazoles 5 (where R^5 is hydroxyl and R^6 is hydrido). Some of the suitable solvents for this reaction are isopropanol, acetone and dimethylformamide. The reaction may be carried out at temperatures of about 20°C to about 90°C. In step 3, the 4,5-dihydroimidazoles 5 may be dehydrated in the presence of an acid catalyst such as 4-toluenesulfonic acid or mineral acids to form the 1,2-disubstituted imidazoles 6 of the invention. Suitable solvents for this dehydration step are e.g., toluene, xylene and benzene. Trifluoroacetic acid can be used as solvent and catalyst for this dehydration step.

In some cases (e.g., where R^3 = methyl or phenyl) the intermediate 5 may not be readily isolable. The reaction, under the conditions described above, proceeds to give the targeted imidazoles directly.

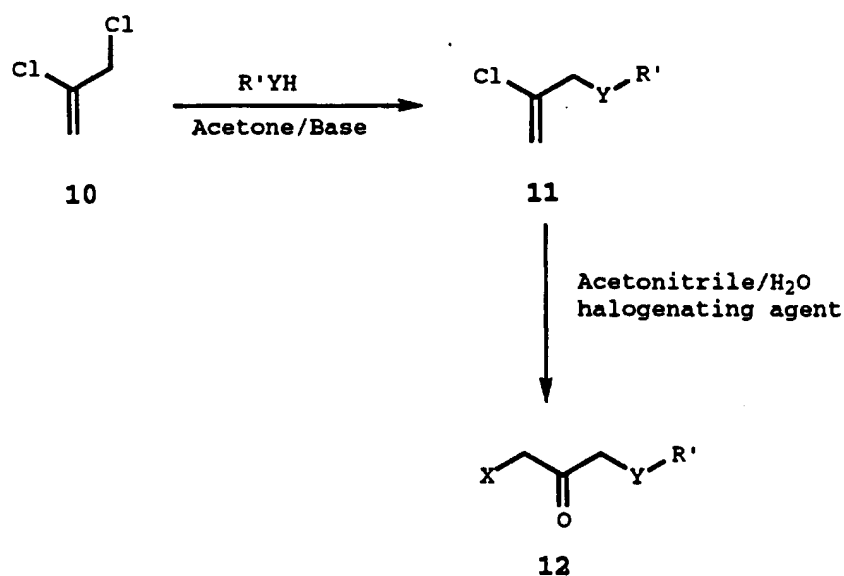
Scheme II



Scheme II shows alternative methods of forming amidines 3. Amidines 3 are also available by the two step conversion of amide 7 (R^2CONHR^1 formed by the

conversion of primary amine 2). In Step 1; the amide 7 is converted to the corresponding imidoyl chloride by treatment with a halogenating agent such as phosphorus oxychloride. In step two, treatment of the imidoyl chloride with ammonia forms the desired amidine 3. In addition, amidines 3 may also be obtained by conversion of primary amides 8 (e. g., R^2CONH_2) or nitriles 1 (R^2CN) to their corresponding iminothioethers or iminoethers, (9 where X is sulfur and oxygen, respectively) followed by reaction with amine 2 R^1NH_2 .

Scheme III



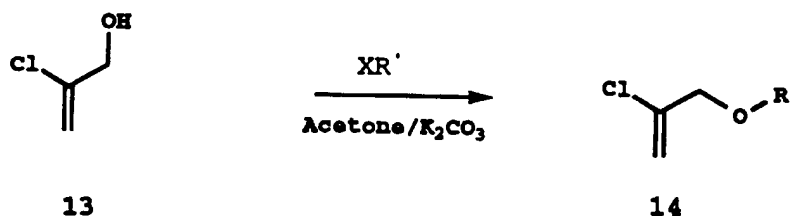
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Scheme III shows the two step method of preparing certain 2-halo-ketones 12 (compound 4 from Scheme I where X is bromo or chloro, R^3 is $-CH_2YR'$ [Y is oxygen, sulfur or $-NH$] and R^4 is hydrido) which are not commercially available, from 1,2-dihalo-propenes 10. In step 1, 2,3-dichloro-1-propene 10 is added to a mixture of alcohol, amine or mercaptan ($R'YH$) and base, such as potassium carbonate in acetone, to form the 2-chloropropene 11, where R' is an alkyl or aryl

25

group and Y is an oxygen, nitrogen or sulfur atom. In step 2, the 2-chloropropene 11 is converted to 2-haloketones 12 via a method as described by H. E. Morton and M. R. Leanna (*Tet. Letters*, **34**, 4481 (1993)).

Scheme IV



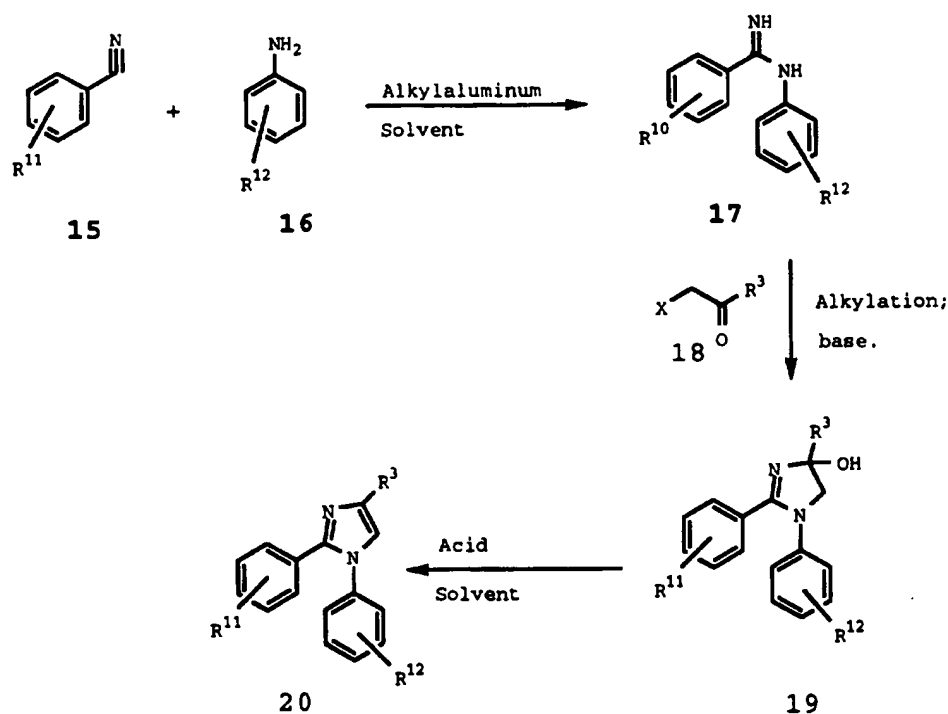
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Scheme IV shows a method of forming 2-chloropropenes 14 (compound 11 in Scheme III where Y is oxygen). The 2-chloro-2-propen-1-ol 13 is added to a mixture of an alkyl, aralkyl or heteroaralkyl halide (XR') and base, such as potassium carbonate in acetone, to form the 2-chloropropene 14.

Alternatively, 2-chloropropenes 14 can be formed from the corresponding 2,3-dichloro-1-propenes 10 (Scheme III) by reaction with a metal alkoxide in an appropriate solvent. Sodium methoxide in methanol is an example of one such alkoxide and solvent.

20

Scheme V



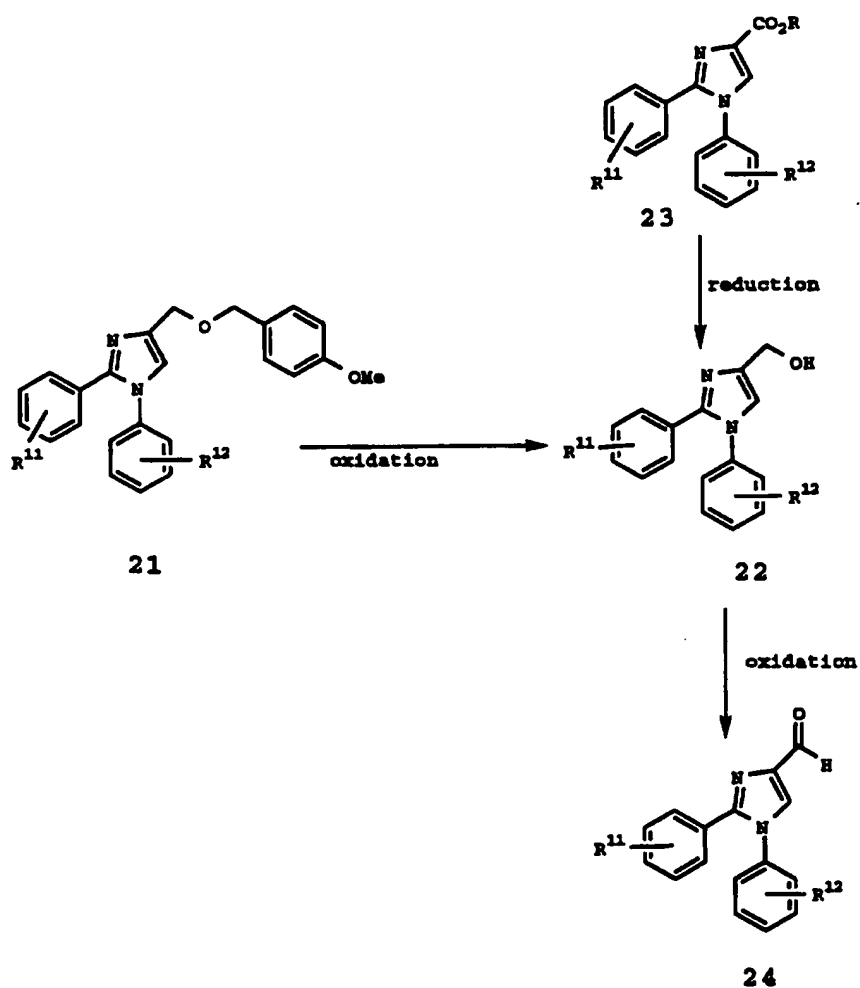
- 5 Scheme V shows the three step preparation of 1,2-
 diarylimidazoles 20 of the present invention. In
 step 1, the reaction of substituted benzonitriles 15
 with substituted anilines 16 in the presence of
 alkylaluminum reagents such as trimethylaluminum,
 10 triethylaluminum, dimethylaluminum chloride,
 diethylaluminum chloride gives amidines 17. In step
 2, the reaction of amidines 17 with haloketones 18
 (compound 4 in Scheme I where X is Br or Cl and R⁴ is
 hydrido) in the presence of bases, such as sodium
 15 bicarbonate, potassium carbonate, sodium carbonate,
 potassium bicarbonate or hindered tertiary amines such
 as *N,N'*-diisopropylethylamine, gives the 1,2-diaryl-
 4,5-dihydro-imidazoles 19. Some of the suitable
 solvents for this reaction are isopropanol, acetone
 20 and dimethylformamide. The reaction may be carried
 out at a temperature between about 20°C to about 90°C.
 In step 3, the 1,2-diaryl-4,5-dihydro-imidazoles 19

may be dehydrated in the presence of an acid catalyst such as 4-toluenesulfonic acid to form the 1,2-diarylimidazoles 20 of the present invention.

Suitable solvents for this dehydration step are, for
5 example, toluene, xylene and benzene. Trifluoroacetic acid can be used as solvent and catalyst for this dehydration step.

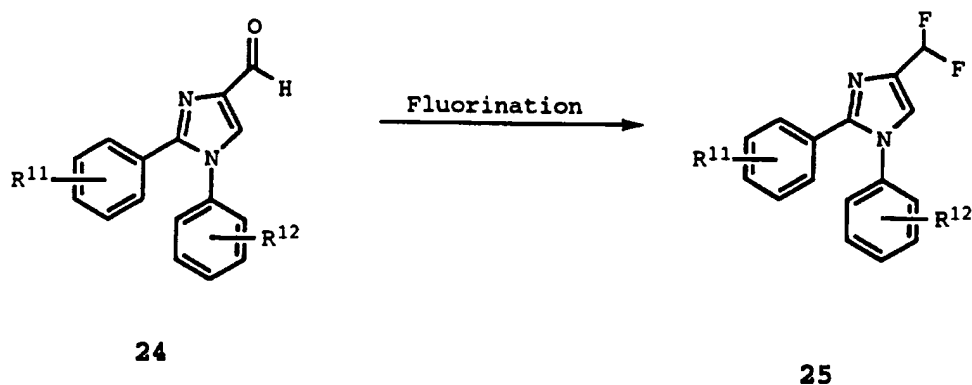
In some cases (e.g., where R^3 is methyl or
10 phenyl), the intermediate 19 may not be readily isolable. The reaction, under the conditions described above, proceeds to give the targeted imidazoles 20 directly.

Scheme VI



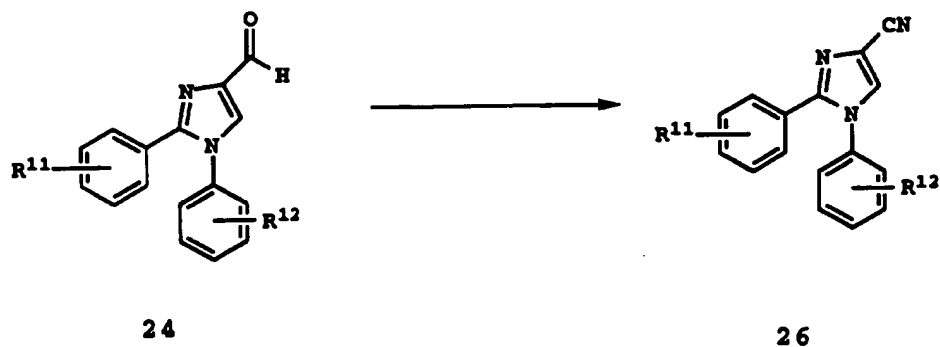
5 Scheme VI shows the formation of 4-hydroxymethyl
imidazoles 22 and 4-formyl-imidazoles 23 from
benzyloxy-protected imidazoles 21 and from 4-
carboalkoxy imidazoles 23. In step 1, the oxidative
deprotection of 4-methoxybenzyl group in 21, such as
10 with ceric ammonium nitrate, gives the hydroxymethyl
imidazoles 22. Alternatively, the alkoxycarbonyl
group of 23 may be reduced to the hydroxymethyl
group. Suitable reducing agents include lithium
borohydride. In step 2, the hydroxymethyl imidazoles
15 22 are oxidized, for example, with pyridinium
chlorochromate, to give the 4-formyl-imidazoles 24.

Scheme VII



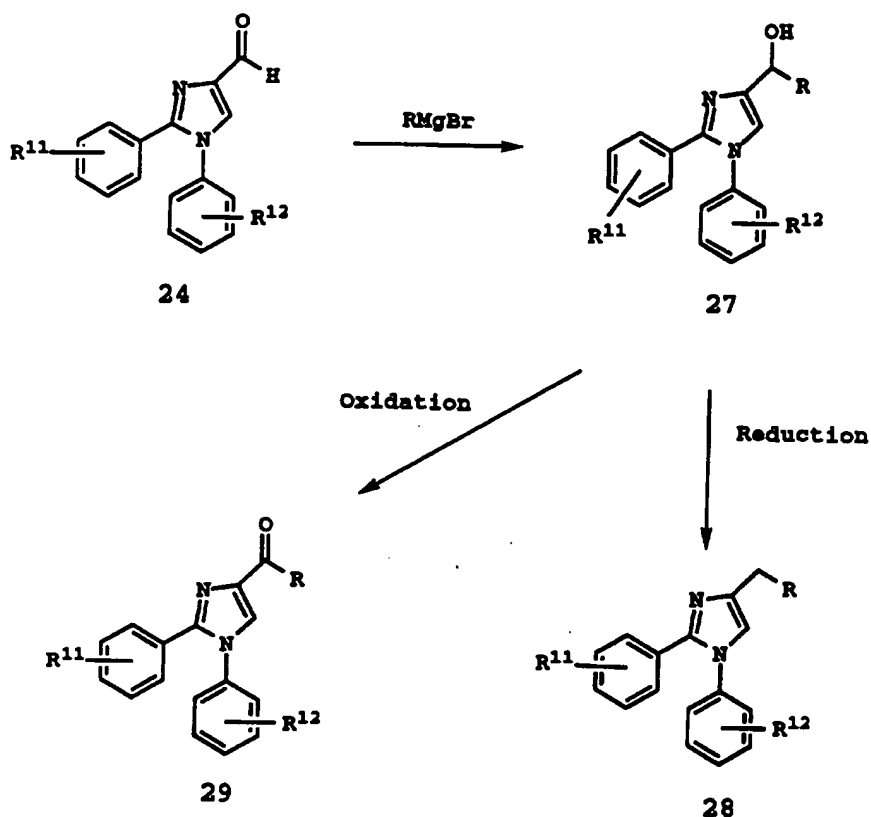
5
Scheme VII shows the formation of 4-
difluoromethyl-imidazoles **25** from 4-formyl-imidazoles
24. The 4-formyl-imidazoles **24** are converted to
desired 4-difluoromethyl-imidazoles **25** by direct
10 fluorination using the known reagents such as SF₄ or
diethylaminosulfur trifluoride (DAST). For discussion
of the reaction and the representative procedures, see
e.g., *Organic Reactions*, **34**, 319 (1987), *Organic*
Reactions, **35**, 513 (1988), *Organic Reactions*, **21**, 319
15 (1974) and *Chem. Soc. Reviews*, **16**, 381 (1987).
Alternatively, the imidazoles **25** can be synthesized
by reaction of hydrazones of **24** with N-
bromosuccinimide/pyridinium poly(hydrogen fluoride).
This transformation has been developed by Olah and co-
20 workers (see, *Synlett*, 594 (1990)).

Scheme VIII



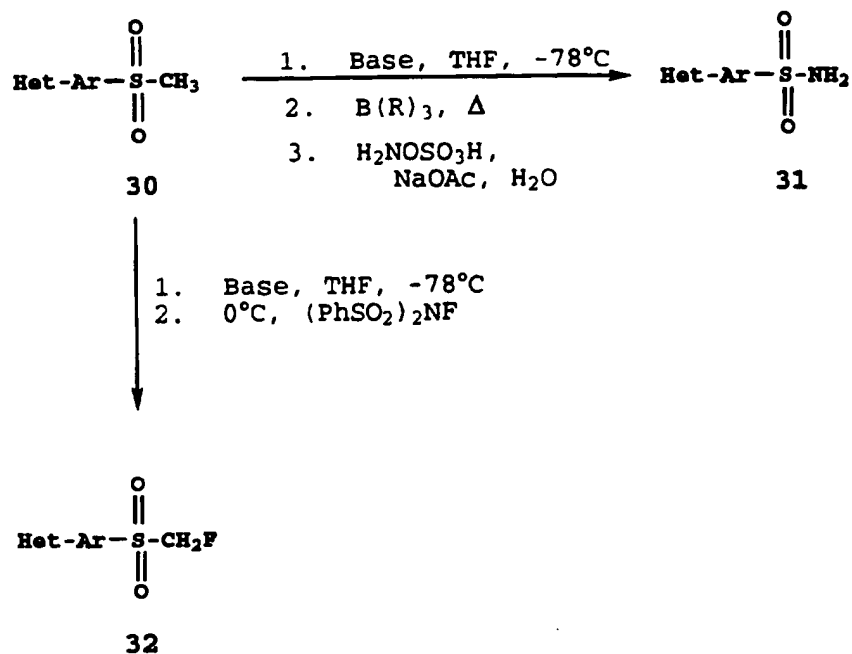
5 Scheme VIII shows the conversion of the 4-formyl-
imidazoles **24** to 4-cyanoimidazoles **26**. The 4-formyl-
imidazoles **24** are converted to the target nitrile
derivatives **26** by following the literature procedures
[see, e.g., *Chem. Letters*, 773 (1984), *Synthesis*, 510
10 (1984), *Tetrahedron Lett.*, 1781 (1976), *Synthesis*, 739
(1981), *Synth. Communications*, **18**, 2179 (1988), *Bull.*
Chem. Soc. Japan, **54**, 1579 (1981), *Synthesis*, 201
(1985), *Synthesis*, 190 (1982), *Synthesis*, 56 (1979),
and the references cited therein].

Scheme IX



- 5 Scheme IX shows other 1,2-diarylimidazoles that
can be synthesized from the 4-formyl-imidazoles 24 in
two steps. In step 1, the 4-formyl-imidazoles 24 are
converted to carbinol derivatives (where R is aralkyl
or alkyl) by addition of Grignard reagents (RMgBr). In
10 step 2, the hydroxy derivatives 27 are reduced by
catalytic hydrogenation (using e.g., Pd/C or Pt/C),
preferably in the presence of a small amount of acid
(e.g., acetic acid or aqueous HCl) to form the alkyl or
aralkyl derivatives 28. Alternatively, the ketones 29
15 are synthesized by oxidation (e.g., using pyridinium
chlorochromate) of the hydroxy derivatives 27.

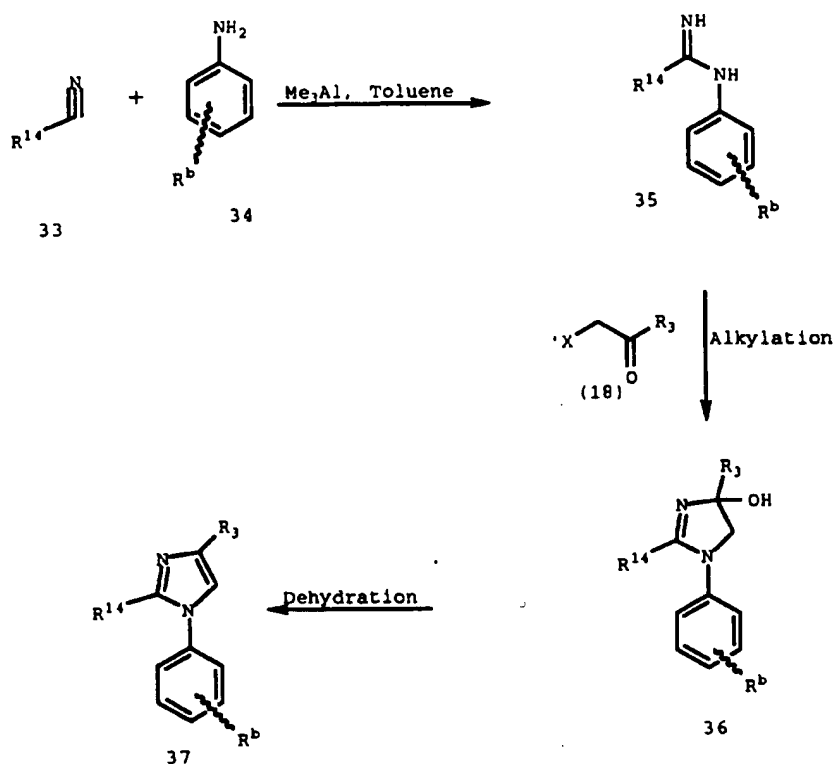
Scheme X



- 5 Synthetic Scheme X shows the three step procedure used to prepare sulfonamide antiinflammatory agents 31 and the two step procedure used to prepare fluoromethyl sulfone antiinflammatory agents 32 from their corresponding methyl sulfones 30. In step one,
- 10 THF solutions of the methyl sulfones 30 at -78°C are treated with a base such as alkylolithium reagents, lithioamides and Grignard reagents. Examples of such bases include n-butyllithium, methyllithium, lithium diisopropylamide (LDA), butylmagnesium chloride,
- 15 phenylmagnesium bromide and methylmagnesium chloride. In step two, the anions generated in step one are treated with an organoborane, e.g., triethylborane, tributylborane, etc., at -78°C then warmed to ambient temperature prior to stirring at reflux. An
- 20 alternative to the boron chemistry involves room temperature alkylation, such as with haloalkyltrialkylsilanes, followed by treatment with silylalkyl-elimination agents. Examples of such

haloalkyltrialkylsilanes include trimethylsilylmethylhalides such as (iodomethyl)trimethylsilane and (chloromethyl)trimethylsilane. Suitable silylalkyl-
5 elimination agents include compounds which produce a fluoride ion. Examples of such compounds include alkylammonium fluorides and cesium fluoride. tetrabutylammonium fluoride (1M in THF) is preferred. The deprotonation of sulfone is conveniently carried
10 out in the temperature range of about -70°C to about 25°C, preferably at about 0°C. The formation of silylalkylsulfone is conveniently carried out in the temperature range of about 0°C to about 35°C, preferably at about 20°C. In step three, an aqueous
15 solution of sodium acetate and hydroxylamine-O-sulfonic acid is added to provide the corresponding sulfonamide antiinflammatory agents 31 of this invention. Alternatively, the anion solutions generated in step one may be warmed to 0°C and treated
20 with N-fluorodibenzenesulfonamide to provide the corresponding fluoromethyl sulfone antiinflammatory agents 32 of this invention.

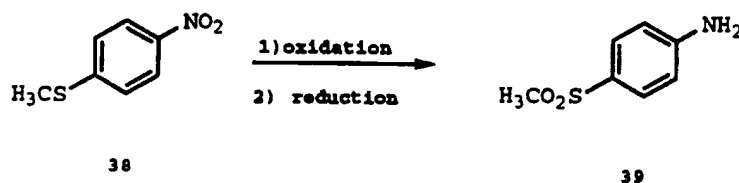
Scheme XI



- 5 1-Phenyl-2-heterocycloimidazoles of the current invention 37 are synthesized by following the generic synthesis shown in Scheme XI. The reaction of a substituted heterocyclonitrile 33 with substituted anilines 34 (where R^b is as defined above for aryl and heteroaryl radicals) in the presence of alkylaluminum reagents such as trimethylaluminum, triethylaluminum, dimethylaluminum chloride, diethylaluminum chloride gives the amidine 35. The reaction of amidine 35 with a 2-halo-ketone derivative 18 ($X' = \text{Br or Cl}$) in the presence of bases such as sodium bicarbonate, potassium carbonate, sodium carbonate, potassium bicarbonate or *N,N'*-diisopropylethylamine gives the alkylated product 36. Some of the suitable solvents for this reaction are *i*-propanol, acetone and dimethylformamide. The reaction may be carried out at 20 to 90°C. The intermediate 36 may be dehydrated in the presence of an
- 10
- 15
- 20

acid catalyst such as 4-toluenesulfonic acid to give the targeted 1,2-diarylimidazoles 37. Suitable solvents for this dehydration step are e.g., toluene, xylene and benzene. Alternatively, trifluoroacetic acid may be used both as solvent and catalyst in this dehydration step.

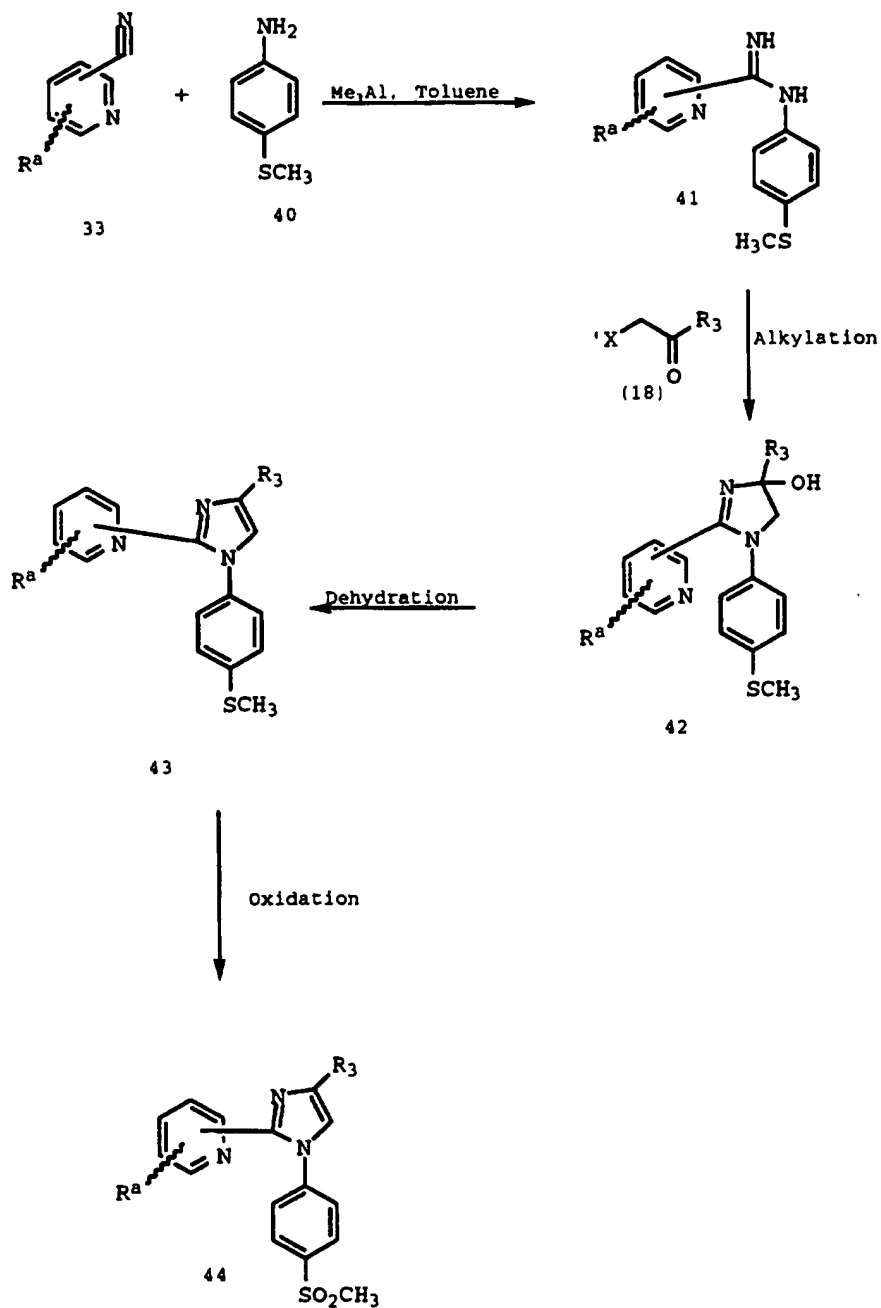
Scheme XII



10

Scheme XII shows a two step method of forming sulfonyl anilines 39 from nitro compounds 38. In step one, the 4-methylthio-nitrobenzene 38 is oxidized to the sulfone with an oxidizing reagent such as hydrogen peroxide, Oxone[®] or MCPBA. In step 2, the 4-methylsulfonyl-nitrobenzene is reduced to the corresponding aniline 39.

Scheme XIII

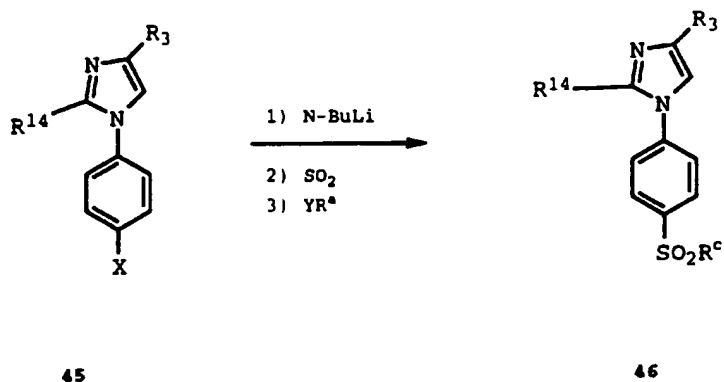


5 Synthetic Scheme XIII describes an alternative method of forming 1-aryl-2-pyridyl-imidazoles **44** from 4-alkylthioanilines **40**. The reaction of a substituted cyanopyridine **33** (where R^a is as defined above for aryl

and heteroaryl radicals) with substituted anilines 40 in the presence of alkylaluminum reagents such as trimethylaluminum, triethylaluminum, dimethylaluminum chloride, diethylaluminum chloride gives the amidine 41. Alternatively, amidine 41 may be synthesized by reaction of aniline 40 first with a suitable base, and then with nitrile 33. Examples of suitable bases include sodium hydride, sodium methoxide, n-butyllithium and lithium diisopropylamide. These reactions may be run in solvents such as dimethyl sulfoxide, tetrahydrofuran, dimethoxyethane and methanol or the like. The reaction of amidine 41 with a 2-halo-ketone derivative 18 ($X' = \text{Br or Cl}$) in the presence of bases such as sodium bicarbonate, potassium carbonate, sodium carbonate, potassium bicarbonate or *N,N'*-diisopropylethylamine gives the alkylated product 42. Some of the suitable solvents for this reaction are *i*-propanol, acetone and dimethylformamide. The reaction may be carried out at 20 to 90°C. The intermediate 42 is dehydrated in the presence of an acid catalyst such as 4-toluenesulfonic acid to give the 1-(4-alkylthio)aryl-2-pyridylimidazoles 43. Suitable solvents for this dehydration step are e.g., toluene, xylene and benzene. Oxidation of the alkylthio 43, with an oxidizing reagent such as hydrogen peroxide, Oxone® or MCPBA, yields the sulfones 44.

100

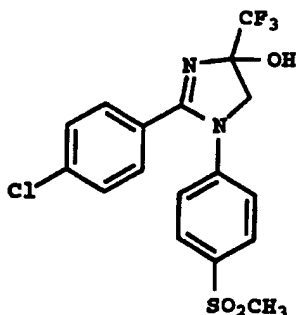
Scheme XIV



5 Scheme XIV shows a method of forming sulfones and
sulfonamides 46 from the corresponding 1-
phenylimidazoles 45, where X is a leaving group such
as halo. Treatment of 45 with base, such as butyl
lithium, followed by addition of sulfur dioxide and a
10 substituted alkyl or amine yields the corresponding
sulfone or sulfonamide 46 (where R^a is alkyl or
amino).

 The following examples contain detailed
descriptions of the methods of preparation of
15 compounds of Formula I-V. These detailed descriptions
fall within the scope, and serve to exemplify, the
above described General Synthetic Procedures which
form part of the invention. These detailed
descriptions are presented for illustrative purposes
20 only and are not intended as a restriction on the
scope of the invention. All parts are by weight and
temperatures are in Degrees centigrade unless
otherwise indicated. All compounds showed NMR spectra
consistent with their assigned structures. In some
25 cases, the assigned structures were confirmed by
nuclear Overhauser effect (NOE) experiments.

Example 1



5 2-(4-Chlorophenyl)-4-hydroxy-1-[4-(
 (methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-
 dihydro-1H-imidazole

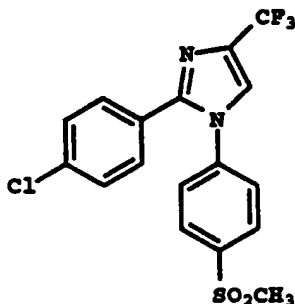
10 Step 1: Preparation of 4-chloro-N-[4-(
 (methylsulfonyl)phenyl]benzenecarboximidamide

 To a suspension of 4-(methylsulfonyl)aniline (7 g,
 41 mmol) in toluene (400 mL), trimethylaluminum (2M
 solution in toluene, 30.5 mL, 61 mmol) was added over
 15 minutes. The reaction mixture was warmed to room
15 temperature and stirred for 2.5 hours. A solution of 4-
 chlorobenzonitrile (11.3 g, 82 mmol) in toluene (200
 mL) was added over 10 minutes and the reaction mixture
 was heated to 80-85°C. After 16 hours, the reaction
 mixture was cooled to room temperature and poured over
20 a slurry of silica gel in chloroform. After filtration,
 the residue was washed with a mixture of methylene
 chloride/methanol. The combined filtrates were
 concentrated in vacuo and the resulting yellowish solid
 was stirred with a mixture of hexane/ether (2/1, 1000
25 mL). The intermediate was filtered and washed with more
 of hexane/ether (2/1). The pale yellow solid 4-chloro-
 N-[4-(methylsulfonyl)phenyl] benzenecarboximidamide
 (10.93 g, 86%) was used in the next reaction without
 further purification: mp (DSC) 191°C. Anal. Calc'd. for
30 C₁₄H₁₃N₂SO₂Cl: C, 54.46, H, 4.24, N, 9.07. Found: C,
 54.42, H, 4.30, N, 9.07.

Step 2: Preparation of 2-(4-chlorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazole

To a mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide from Step 1 (8 g, 26 mmol) and sodium bicarbonate (4.36 g, 52 mmol) in isopropanol (240 mL), 3-bromo-1,1,1-trifluoroacetone (5.4 mL, 52 mmol) was added. After heating the reaction mixture at 75-80°C for 24 hours, the solvent was removed. The residue was redissolved in methylene chloride and washed with water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product (16.2 g) was purified by chromatography (silica gel, hexane/ethyl acetate, 55/45) to give pure 2-(4-chlorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazole (6.7 g, 62%) as a white solid: Anal. Calc'd. for C₁₇H₁₄N₂SO₃ClF₃: C, 48.75, H, 3.37, N, 6.69. Found: C, 48.56, H, 3.22, N, 6.51.

Example 2



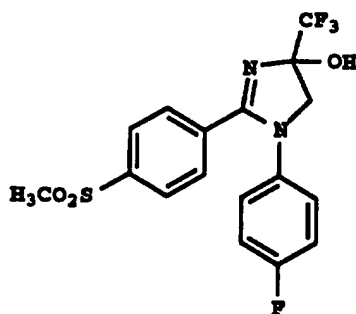
2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole

A mixture of 2-(4-chlorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazole from Example 1 (6.2 g, 15.4 mmol) and *p*-toluenesulfonic acid monohydrate (0.9 g, 4.7

mmol) in toluene (300 mL) was heated to reflux for 84 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude residue was redissolved in methylene chloride and washed with
5 water, aqueous sodium bicarbonate and brine. After drying (Na₂SO₄), filtration and concentrating in vacuo, the crude mixture was purified by chromatography on silica gel using hexane/ethyl acetate (1/1) to give
10 pure 2-(4-chlorophenyl)-1-[4-(methanesulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (4.21 g, 71%) as a white solid: mp (DSC) 183°C. Anal. Calc'd. for C₁₇H₁₂N₂SO₂F₃Cl: C, 50.94, H, 3.02, N, 6.99. Found: C, 50.64, H, 3.03, N, 6.85.

15

Example 3



20 1-(4-Fluorophenyl)-4-hydroxy-
2-[4-(methanesulfonyl)phenyl]-4-
(trifluoromethyl)-4,5-dihydro-1H-imidazole

Step 1: Preparation of 4-methanesulfonyl-N-[4-chlorophenyl]benzenecarboximidamide

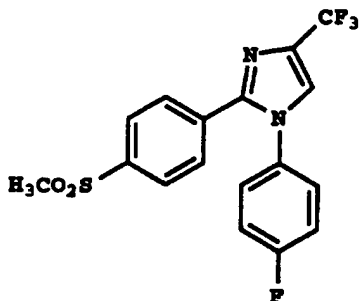
25 To a suspension of 4-fluoroaniline (4 mL, 40 mmol) in toluene (120 mL), trimethylaluminum (2M solution in toluene, 21 mL, 42 mmol) was added over 15 minutes. The reaction mixture was warmed to room temperature and stirred for 3 hours. A solution of 4-
30 (methanesulfonyl)benzonitrile (7.65 g, 40 mmol) in methylene chloride (100 mL) was added over 10 minutes

and the reaction mixture was heated to 70-75°C. After 48 hours, the reaction mixture was cooled to room temperature and poured over a slurry of silica gel in chloroform. After filtration, the residue was washed
5 with a mixture of methylene chloride/methanol. The combined filtrates were concentrated in vacuo and the resulting crude intermediate (7.7 g) was purified by chromatography [silica gel, hexane/ethyl acetate, 25/75] to give 4-methylsulfonyl-N-[4-
10 chlorophenyl]benzenecarboximidamide (4.1 g, 35%) as a white solid: mp (DSC) 182°C. Anal. Calc'd. for $C_{14}H_{13}N_2SO_2F$: C, 57.52, H, 4.48, N, 9.58, S, 10.97. Found: C, 57.37, H, 4.69, N, 9.21, S, 10.69.

15 Step 2: Preparation of 1-(4-fluorophenyl)-4-hydroxy-2-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazole

To a mixture of 4-methylsulfonyl-N-[4-chlorophenyl]benzenecarboximidamide from Step 1 (1 g, 3.42 mmol) and sodium bicarbonate (575 mg, 6.85 mmol)
20 in isopropanol (30 mL), 3-bromo-1,1,1-trifluoroacetone (5.9 g, 25 mmol) was added. After heating the reaction mixture at 80-90°C for 24 hours, the solvent was removed. The residue was redissolved in methylene
25 chloride and washed with water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product (2.34 g) was purified by chromatography [silica gel, hexane/ethyl acetate, 1/1] to give 1-(4-fluorophenyl)-4-hydroxy-2-
30 [4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazole (650 mg, 47%) as a white solid: mp (DSC) 209°C. Anal. Calc'd. for $C_{17}H_{14}N_2SO_3F_4$: C, 50.75, H, 3.51, N, 6.96. Found: C, 51.11, H, 3.86, N, 6.57.

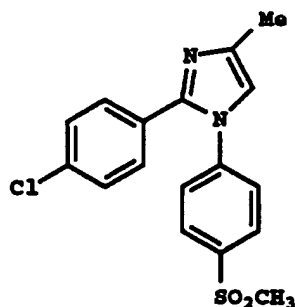
Example 4



5 **1-(4-Fluorophenyl)-2-[4-(methanesulfonyl)phenyl]-**
 4-(trifluoromethyl)-1H-imidazole

A mixture of 1-(4-fluorophenyl)-4-hydroxy-2-[4-(methanesulfonyl)phenyl]-4,5-dihydro-1H-imidazole (Example 3) (770 mg, 1.9 mmol) and *p*-toluenesulfonic acid monohydrate (88 mg) in toluene (80 mL) was heated to reflux for 20 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude residue was redissolved in methylene chloride and washed with water, aqueous sodium bicarbonate and brine. After drying (Na₂SO₄), filtration and concentration *in vacuo*, the crude mixture (520 mg) was purified by chromatography on silica gel using hexane/ethyl acetate (1/1) to give pure 1-(4-fluorophenyl)-2-[4-(methanesulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (328 mg, 44%) as a white solid: mp (DSC) 183°C. Anal. Calc'd. for C₁₇H₁₂N₂SO₂F₄: C, 53.13, H, 3.15, N, 7.29. Found: C, 53.20, H, 3.22, N, 7.18.

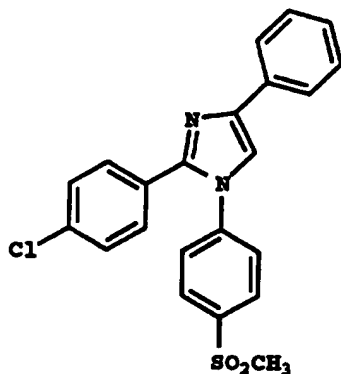
Example 5



5 **2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-**
 4-methyl-1H-imidazole

To a mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Example
10 1, Step 1) (240 mg, 0.78 mmol) and sodium bicarbonate (131 mg, 1.56 mmol) in isopropanol (20 mL), excess
chloroacetone (1.5 mL) was added. After heating to
reflux, the reaction mixture for 72 hours, the solvent
was removed. The residue was redissolved in methylene
15 chloride and washed with aqueous sodium bicarbonate and
water. The organic fractions were combined, dried over
sodium sulfate, filtered and concentrated in vacuo. The
crude product (370 mg) was purified by chromatography
(silica gel, hexane/ethyl acetate, 25/75) to give pure
20 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-
methyl-1H-imidazole (160 mg, 67%): mp (DSC) 166°C. Anal
Calc'd. for C₁₇H₁₅N₂SO₂Cl C, 58.87, H, 4.36, N, 8.08
Found: C, 58.78, H, 4.62, N, 7.99.

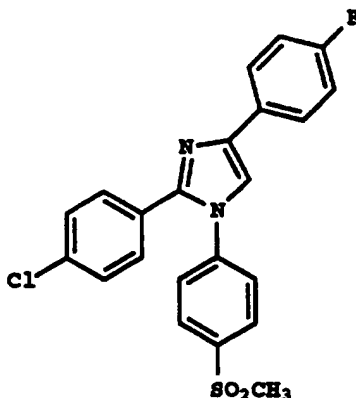
Example 6



5 2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-
4-phenyl-1H-imidazole

To a mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Example
10 1, Step 1) (400 mg, 1.29 mmol) and sodium bicarbonate (216 mg, 2.59 mmol) in isopropanol (25 mL), 2-bromoacetophenone (780 mg, 3.87 mmol) was added. After heating the reaction mixture at 55°C for 20 hours, the solvent was removed. The residue was redissolved in
15 methylene chloride and washed with aqueous sodium bicarbonate and water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product (1.2 g) was purified by chromatography on silica gel with
20 toluene/ethyl acetate (75/25) to give pure 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole (300 mg, 57%) as a white solid: mp (DSC) 202°C. Anal. Calc'd. for C₂₂H₁₇N₂SO₂Cl: C, 63.78, H, 4.28, N, 6.76, S, 7.74. Found: C, 63.69, H, 4.11, N, 6.68, S, 7.65.
25

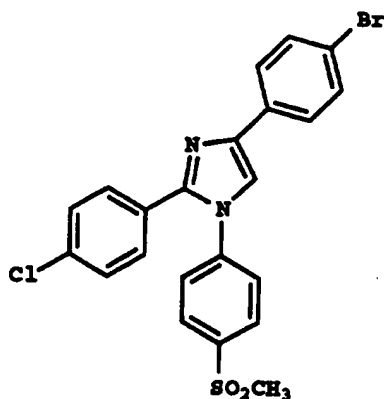
Example 7



5 **2-(4-Chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole**

To a mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Example
10 1, Step 1) (400 mg, 1.29 mmol) and sodium bicarbonate (216 mg, 2.59 mmol) in isopropanol (25 mL), 2-chloro-4'-fluoroacetophenone (670 mg, 3.87 mmol) was added. After heating the reaction mixture at 80-85°C for 48 hours, the solvent was removed. The residue was
15 redissolved in methylene chloride and washed with aqueous sodium bicarbonate and water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product (800 mg) was purified by chromatography (silica gel,
20 hexane/ethyl acetate, 1/1) to give 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (200 mg, 36%) as a pale yellow solid: mp (DSC) 180°C. Anal. Calc'd. for C₂₂H₁₆N₂SO₂FCl: C, 61.90, H, 3.78, N, 6.56, S, 7.51. Found: C, 61.92, H, 3.74, N, 6.43, S, 7.62.
25

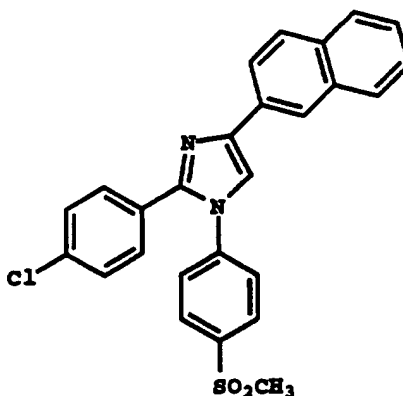
Example 8



5 **4-(4-Bromophenyl)-2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole**

To a mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Example 1, Step 1) (400 mg, 1.29 mmol) and sodium bicarbonate (216 mg, 2.59 mmol) in isopropanol (30 mL), 2, 4'-dibromoacetophenone (720 mg, 2.58 mmol) was added. After heating the reaction mixture at 80-85°C for 18 hours, the solvent was removed. The residue was redissolved in methylene chloride and washed with aqueous sodium bicarbonate and water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product (810 mg) was purified by chromatography (silica gel, hexane/ethyl acetate, 6/4) to give 4-(4-bromophenyl)-2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (400 mg, 64%) as a pale yellow solid: mp 145-48°C. Anal. Calc'd. for C₂₂H₁₆N₂SO₂BrCl: C, 54.17, H, 3.31, N, 5.74, S, 6.57. Found: C, 54.41, H, 3.33, N, 5.50, S, 6.52.

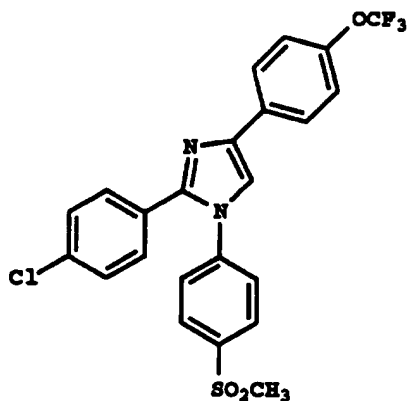
Example 9



5 2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-
4-(2-naphthyl)-1H-imidazole

To a mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Example
10 1, Step 1) (400 mg, 1.29 mmol) and sodium bicarbonate
(216 mg, 2.59 mmol) in isopropanol (30 mL), 2-bromo-2'-
acetophenone (970 mg, 3.89 mmol) was added. After
heating the reaction mixture at 80-85°C for 20 hours,
the solvent was removed. The residue was redissolved
15 in methylene chloride and washed with aqueous sodium
bicarbonate and water. The organic fractions were
combined, dried over sodium sulfate, filtered and
concentrated in vacuo. The crude product (1.2 g) was
purified by chromatography (silica gel, hexane/ethyl
20 acetate, 6/4) to give 2-(4-chlorophenyl)-1-[4-
(methylsulfonyl)phenyl]-4-(2-naphthyl)-1H-imidazole
(318 mg, 54%) as a pale yellow solid: mp 204-206°C.
Anal Calc'd. for C₂₆H₁₉N₂SO₂Cl: C, 68.04, H, 4.17, N,
6.10, S, 6.99. Found: C, 67.65, H, 4.19, N, 5.96, S,
25 7.10.

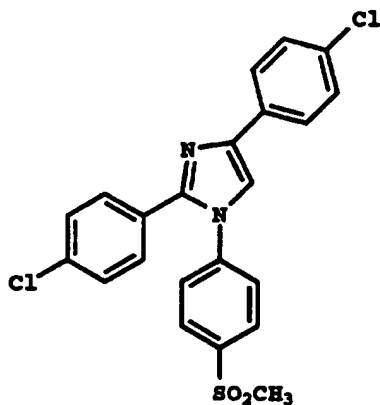
Example 10



5 **2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-**
 4-[4-(trifluoromethoxy)phenyl]-1H-imidazole

To a mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Example 1, Step 1) (700 mg, 2.24 mmol) and sodium bicarbonate (376 mg, 4.48 mmol) in isopropanol (25 mL), 4-(trifluoromethoxy)phenacyl bromide (950 mg, 3.36 mmol) was added. After heating the reaction mixture at 80-85°C for 22 hours, the solvent was removed. The residue was redissolved in methylene chloride and washed with aqueous sodium bicarbonate and water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by chromatography (silica gel, hexane/ethyl acetate, 6/4) to give 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-[4-(trifluoromethoxy)phenyl]-1H-imidazole (467 mg, 42%) as a pale yellow solid: mp 95-97°C. Anal. Calc'd. for C₂₃H₁₆N₂SO₃F₃Cl: C, 56.05, H, 3.27, N, 5.68, S, 6.51. Found: C, 55.90, H, 3.04, N, 5.62, S, 6.74.

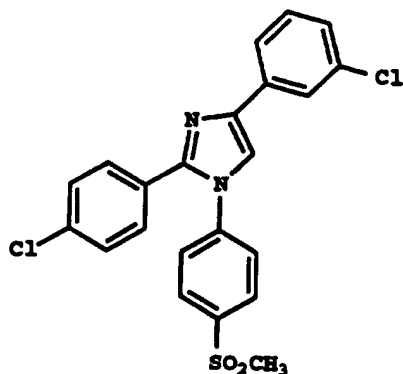
Example 11



5 **2,4-Bis(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole**

To a mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Example 1, Step 1) (700 mg, 2.24 mmol) and sodium bicarbonate (376 mg, 4.48 mmol) in isopropanol (30 mL), 4-chlorophenacyl bromide (1.05 g, 4.48 mmol) was added. After heating the reaction mixture at 80-85°C for 18 hours, the solvent was removed. The residue was redissolved in methylene chloride and washed with aqueous sodium bicarbonate and water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by chromatography (silica gel, hexane/ethyl acetate, 6/4) to give 2,4-bis-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (545 mg, 55%) as a pale yellow solid: mp 169-171°C. Anal. Calc'd. for C₂₂H₁₆N₂SO₂Cl₂: C, 59.60, H, 3.64, N, 6.32, S, 7.23. Found: C, 59.86, H, 3.80, N, 6.10, S, 7.27.

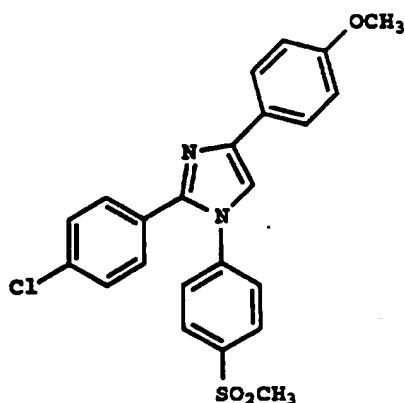
Example 12



5 **2-(4-Chlorophenyl)-4-(3-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole**

To a mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Example
10 1, Step 1) (700 mg, 2.24 mmol) and sodium bicarbonate (376 mg, 4.48 mmol) in isopropanol (35 mL), 3-chlorophenacyl bromide (1.05 g, 4.48 mmol) was added. After heating the reaction mixture at 80-85°C for 18 hours, the solvent was removed. The residue was
15 redissolved in methylene chloride and washed with aqueous sodium bicarbonate and water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by chromatography (silica gel,
20 hexane/ethyl acetate, 6/4) to give 2-(4-chlorophenyl)-4-(3-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (525 mg, 53%) as a pale yellow solid: mp 156-159°C. Anal Calc'd. for C₂₂H₁₆N₂SO₂Cl₂: C, 59.60, H, 3.69, N, 6.32, S, 7.23. Found: C, 59.43, H, 3.59, N,
25 6.15, S, 7.16.

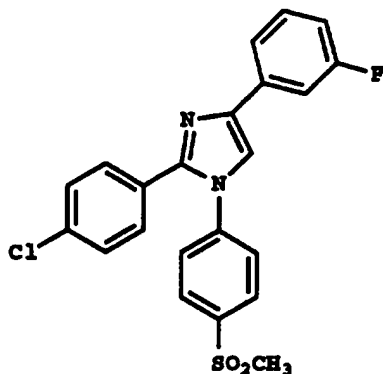
Example 13



5 **2-(4-Chlorophenyl)-4-(4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole**

To a mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Example
10 1, Step 1) (700 mg, 2.24 mmol) and sodium bicarbonate (376 mg, 4.48 mmol) in isopropanol (50 mL), 4-methoxyphenacyl bromide (1.03 g, 4.48 mmol) was added. After heating the reaction mixture at 75-80°C for 20 hours, the solvent was removed. The residue was
15 redissolved in methylene chloride and washed with aqueous sodium bicarbonate and water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by chromatography (silica gel,
20 hexane/ethyl acetate, 6/4) to give 2-(4-chlorophenyl)-4-(4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(4-methoxyphenyl)-1H-imidazole (695 mg, 71%) as a white solid: mp 110-113°C. Anal Calc'd. for C₂₃H₁₉N₂SO₃Cl: C, 62.94, H, 4.36, N, 6.38, S, 7.30. Found: C, 62.54, H,
25 4.43, N, 6.17, S, 7.15.

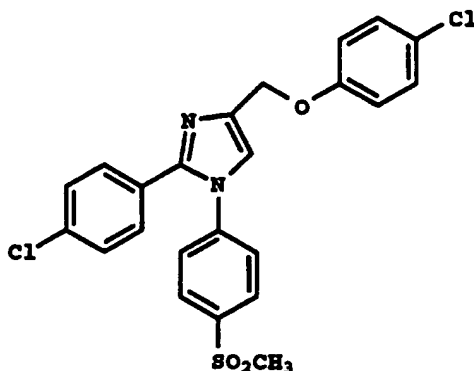
Example 14



5 **2-(4-Chlorophenyl)-4-(3-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole**

To a mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Example
10 1, Step 1) (700 mg, 2.24 mmol) and sodium bicarbonate (376 mg, 4.48 mmol) in isopropanol (30 mL), 3-fluorophenacyl bromide (0.97 g, 4.48 mmol) was added. After heating the reaction mixture at 75-80°C for 18 hours, the solvent was removed. The residue was
15 redissolved in methylene chloride and washed with aqueous sodium bicarbonate and water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by chromatography (silica gel,
20 hexane/ethyl acetate, 6/4) to give 2-(4-chlorophenyl)-4-(3-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (481 mg, 50%) as a white solid: mp 194-196°C. Anal. Calc'd. for C₂₂H₁₆N₂SO₂FCl: C, 61.90, H, 3.78, N, 6.56, S, 7.51. Found: C, 61.71, H, 3.59, N, 6.42, S, 7.69.
25

Example 15



5 **2-(4-Chlorophenyl)-4-[(4-chlorophenoxy)methyl]-**
 1-[4-(methylsulfonyl)phenyl]-1H-imidazole

Step 1: Preparation of 1-(4-chlorophenoxy)-2-chloro-
 2-propene

10 To a mixture of 4-chlorophenol (6.1 g, 47.4 mmol) and potassium carbonate (13.1 g, 94.7 mmol) in acetone (200 mL), 2,3-dichloropropene (6.6 mL, 71 mmol) was added. After heating to reflux the reaction mixture for 48 hours, the reaction mixture was cooled and filtered.

15 The residue was washed with more acetone and the combined filtrates were concentrated in vacuo. The crude pale brown liquid (11.5 g) was purified by chromatography (silica gel, hexane/ethyl acetate, 85/15) to give 1-(4-chlorophenoxy)-2-chloro-2-propene

20 (8.9 g, 98%) as a white liquid: Anal. Calc'd. for $C_9H_8OCl_2$: C, 53.23, H, 3.97. Found: C, 53.09, H, 3.95.

Step 2: Preparation of 1-bromo-3-[(4-
 chlorophenoxy)phenyl]-2-propanone

25 To a turbid solution of 1-(4-chlorophenoxy)-2-chloro-2-propene from Step 1 (3 g, 15.7 mmol) in acetonitrile/water (4/1, 100 mL), *N*-bromosuccinimide (4.84 g, 31.4 mmol) was added in one lot. A catalytic amount of 48% HBr (40 μ l) was added to the reaction and

30 the yellowish orange mixture was stirred at room temperature. After 24 hours, the reaction mixture was

diluted with ether and washed with 5% w/v of sodium thiosulfate. The organic layer was separated and washed with saturated sodium bicarbonate and brine. After drying (MgSO₄), filtration and concentration *in vacuo*,
5 the crude liquid (4.8 g) was purified by chromatography (silica gel, hexane/ethyl acetate, 80/20) to give crude 1-bromo-3-[(4-chlorophenoxy)phenyl]-2-propanone (2.3 g, 54%) which was used in the next step without further purification.

10

Step 3: Preparation of 2-(4-chlorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-[(4-chlorophenoxy)methyl]-4,5-dihydro-1H-imidazole

To a mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Example
15 1, Step 1) (1 g, 3.24 mmol) and sodium bicarbonate (550 mg, 6.5 mmol) in acetone (100 mL), 1-bromo-3-[(4-chlorophenoxy)phenyl]-2-propanone from Step 2 (1.5 g, 5.8 mmol) was added. After heating to reflux for 24
20 hours, the reaction mixture was filtered, washed with acetone and concentrated *in vacuo*. The crude mixture (2.5 g) was purified by chromatography (silica gel, toluene/ethyl acetate, 1/1) to give 2-(4-chlorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-[(4-chlorophenoxy)methyl]-4,5-dihydro-1H-imidazole (565 mg,
25 35%) as a white solid.

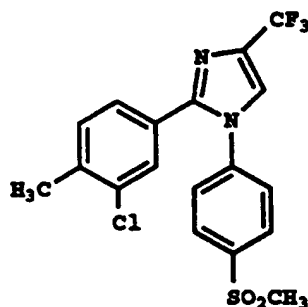
Step 4: Preparation of 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-[(4-chlorophenoxy)methyl]-1H-imidazole

30

A mixture of 2-(4-chlorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-[(4-chlorophenoxy)methyl]-4,5-dihydro-1H-imidazole from Step 3 (750 mg, 1.5 mmol) and *p*-toluenesulfonic acid monohydrate (135 mg) in
35 toluene (100 mL) was heated to reflux for 48 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude residue was redissolved in methylene chloride and washed with

water, aqueous sodium bicarbonate and brine. After drying (Na₂SO₄), filtration and concentration in vacuo, the crude mixture was purified by chromatography on silica gel using hexane/ethyl acetate (1/1) to give 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-[(4-chlorophenoxy)methyl]-1H-imidazole as a white solid: mp (DSC) 173°C. Anal. Calc'd for C₂₃H₁₈N₂Cl₂SO₃•0.25 H₂O: C, 57.81; H, 3.90; N, 5.86; Cl, 14.84. Found: C, 57.67; H, 3.83; N, 5.52; Cl, 15.17.

Example 16



2-(3-Chloro-4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole

Step 1: Preparation of 3-chloro-4-methyl-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide

To a suspension of 4-(methylsulfonyl)aniline (2.82 g, 16.5 mmol) in toluene (150 mL), trimethylaluminum (2M solution in toluene, 12.5 mL, 24.7 mmol) was added over 15 minutes. The reaction mixture was warmed to room temperature and stirred for 2.5 hours. A solution of 3-chloro-4-methylbenzonitrile (5 g, 33 mmol) in toluene (100 mL) was added over 10 minutes and the reaction mixture was heated to 90-95°C. After 20 hours, the reaction mixture was cooled to room temperature and poured over a slurry of silica gel in chloroform. After filtration, the residue was washed with a mixture of methylene chloride/methanol (2/1). The combined filtrates were concentrated in vacuo and the resulting

yellowish solid was stirred with a mixture of hexane/ether (2/1, 700 mL). The intermediate was filtered and washed with more of hexane/ether (2/1).

The pale yellow solid 3-chloro-4-methyl-N-[4-

- 5 (methylsulfonyl)phenyl]benzenecarboximidamide (4.7 g, 88%) was used in the next reaction without further purification: mp (DSC) 179°C. Anal. Calc'd. for $C_{15}H_{15}N_2SO_2Cl$: C, 55.81, H, 4.68, N, 8.68. Found: C, 55.65, H, 4.63, N, 8.59.

10

Step 2: Preparation of 2-(3-chloro-4-methylphenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazole

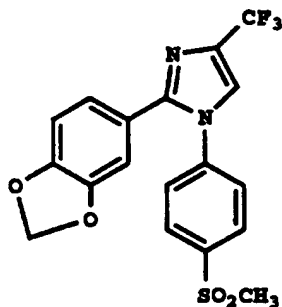
- To a mixture of 3-chloro-4-methyl-N-[4-
- 15 (methylsulfonyl)phenyl]benzenecarboximidamide from Step 1 (2.35 g, 7.3 mmol) and sodium bicarbonate (1.23 g, 14.6 mmol) in isopropanol (100 mL), 3-bromo-1,1,1-trifluoroacetone (5.4 mL, 52 mmol) was added. After heating to reflux the reaction mixture for 24 hours,
- 20 the solvent was removed. The residue was redissolved in methylene chloride and washed with water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude mixture (7.3 g) was purified by chromatography (silica gel,
- 25 toluene/ethyl acetate, 1/1) to give 2-(3-chloro-4-methylphenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazole (0.79 g, 25%) as a white solid: mp 201°C. Anal. Calc'd. for $C_{18}H_{16}N_2SO_3F_3Cl \cdot 0.5 PhCH_3$: C, 53.92, H, 4.21, N, 5.81.
- 30 Found: C, 54.20, H, 4.19, N, 5.67.

Step 3: Preparation of 2-(3-chloro-4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole

- 35 A mixture of 2-(3-chloro-4-methylphenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazole from Step 2 (725 mg, 1.7 mmol) and p-toluenesulfonic acid

monohydrate (150 mg) in toluene (40 mL) was heated to reflux for 48 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude residue was redissolved in methylene chloride and washed with water, aqueous sodium bicarbonate and brine. After drying (Na₂SO₄), filtration and concentration *in vacuo*, the crude mixture (860 mg) was purified by chromatography on silica gel using toluene/ethyl acetate 1/1 to give pure 2-(3-chloro-4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (660 mg, 95%) as a white solid: mp(DSC) 206°C. Anal. Calc'd. for C₁₈H₁₄N₂SO₂F₃Cl: C, 52.12, H, 3.40, N, 6.75, S, 7.73. Found: C, 52.24, H, 3.45, N, 6.64, S, 7.83.

Example 17



5-[1-[4-(Methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]-1,3-benzodioxole

Step 1: Preparation of 3,4-methylenedioxy-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide

To a suspension of (4-methylsulfonyl)aniline (2.82 g, 16.5 mmol) in toluene (150 mL), trimethylaluminum (2M solution in toluene, 12.5 mL, 24.7 mmol) was added over 15 minutes. The reaction mixture was warmed to room temperature and stirred for 2.5 hours. A solution of piperonylnitrile (4.85 g, 33 mmol) in toluene (100 mL) was added over 10 minutes and the reaction mixture was heated to 90-95°C. After 20 hours, the reaction

mixture was cooled to room temperature and poured over a slurry of silica gel in chloroform. After filtration, the residue was washed with a mixture of methylene chloride/methanol (2/1). The combined filtrates were concentrated in vacuo and the resulting yellowish solid was stirred with a mixture of hexane/ether (2/1, 1000 mL). The product was filtered and washed with more of hexane/ether (2/1). The pale yellow solid 3,4-methylenedioxy-N-[4-(methanesulfonyl)phenyl]benzenecarboximidamide (4.8 g, 91%) was used in the next reaction without further purification: mp (DSC) 214°C. Anal. Calc'd. for C₁₅H₁₄N₂SO₄: C, 56.59, H, 4.43, N, 8.80. Found: C, 56.33, H, 4.28, N, 8.66.

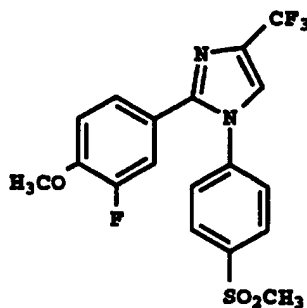
15 Step 2: Preparation of 5-[1-[4-(methanesulfonyl)phenyl]-4-hydroxy-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]-1,3-benzodioxole

To a mixture of 3,4-methylenedioxy-N-[4-(methanesulfonyl)phenyl]benzenecarboximidamide from Step 1 (2.32 g, 7.3 mmol) and sodium bicarbonate (1.23 g, 14.6 mmol) in isopropanol (100 mL), 3-bromo-1,1,1-trifluoroacetone (5.4 mL, 52 mmol) was added. After heating the reaction mixture to reflux for 24 hours, the solvent was removed. The residue was redissolved in methylene chloride and washed with water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude mixture (7.1 g) was purified by chromatography (silica gel, toluene/ethyl acetate, 1/1) to give 5-[1-[4-(methanesulfonyl)phenyl]-4-hydroxy-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]-1,3-benzodioxole (1.46 g, 47%) as a white solid: mp 200-202°C. Anal. Calc'd. for C₁₈H₁₅N₂SO₅F₃•0.25 PhCH₃: C, 52.55, H, 3.80, N, 6.21. Found: C, 52.73, H, 3.78, N, 6.01.

Step 3: Preparation of 5-[1-[4-(methanesulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]-1,3-benzodioxole

A mixture of 5-[1-[4-(methanesulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]-1,3-benzodioxole from Step 2 (1.26 g, 2.9 mmol) and p-toluenesulfonic acid monohydrate (200 mg) in toluene (50 mL) was heated to reflux for 72 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude residue was redissolved in methylene chloride and washed with water, aqueous sodium bicarbonate and brine. After drying (Na₂SO₄), filtration and concentration in vacuo, the crude mixture (1.34 g) was purified by chromatography on silica gel using toluene/ethyl acetate 1/1 to give pure 5-[1-[4-(methanesulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]-1,3-benzodioxole (940 mg, 80%) as a white solid: mp (DSC) 165°C. Anal Calc'd. for C₁₈H₁₃N₂SO₄F₃: C, 52.68, H, 3.19, N, 6.83. Found: C, 53.05, H, 3.19, N, 6.65.

Example 18



2-(3-Fluoro-4-methoxyphenyl)-1-[4-(methanesulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole

Step 1: Preparation of 3-fluoro-4-methoxy-N-[4-(methanesulfonyl)phenyl]benzenecarboximidamide

To a suspension of 4-(methanesulfonyl)aniline (2.82 g, 16.5 mmol) in toluene (150 mL), trimethylaluminum

(2M solution in toluene, 12.5 mL, 24.7 mmol) was added over 15 minutes. The reaction mixture was warmed to room temperature and stirred for 2.5 hours. A solution of 3-fluoro-4-methoxybenzonitrile (5 g, 33 mmol) in toluene (100 mL) was added over 10 minutes and the reaction mixture was heated to 80-85°C. After 20 hours, the reaction mixture was cooled to room temperature and poured over a slurry of silica gel in chloroform. After filtration, the residue was washed with a mixture of methylene chloride/methanol (2/1). The combined filtrates were concentrated in vacuo and the resulting yellowish solid was stirred with a mixture of hexane/ether (2/1, 1000 mL). The intermediate was filtered and washed with more hexane/ether (2/1). The pale yellow solid 3-fluoro-4-methoxy-N-[4-(methylsulfonyl)phenyl] benzenecarboximidamide (3.95 g, 74%) was used in the next reaction without further purification: mp (DSC) 195°C. Anal. Calc'd. for C₁₅H₁₅N₂SO₃F: C, 55.89, H, 4.69, N, 8.69. Found: C, 55.92, H, 4.74, N, 8.53.

Step 2: Preparation of 2-(3-fluoro-4-methoxyphenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazole

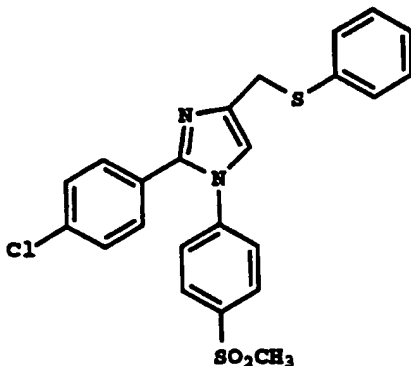
To a mixture of 3-fluoro-4-methoxy-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide from Step 1 (4.15 g, 12.9 mmol) and sodium bicarbonate (2.16 g, 25.8 mmol) in isopropanol (150 mL), 3-bromo-1,1,1-trifluoroacetone (4.8 mL, 45 mmol) was added. After heating the reaction mixture at 70-75°C for 20 hours, the solvent was removed. The residue was redissolved in methylene chloride and washed with water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude mixture (7.8 g) was purified by chromatography (silica gel, toluene/ethyl acetate, 7/3) to give 2-(3-fluoro-4-methoxyphenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazole (3.54 g,

64%) as a white solid: mp (DSC) 210°C. Anal. Calc'd. for $C_{18}H_{16}N_2SO_4F_4 \cdot 0.1 PhCH_3$: C, 50.86, H, 3.83, N, 6.34. Found: C, 50.61, H, 3.64, N, 6.16.

5 Step 3: Preparation of 2-(3-fluoro-4-methoxyphenyl)-
1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-
imidazole

A mixture of 2-(3-fluoro-4-methoxyphenyl)-4-
hydroxy-1-[4-(methylsulfonyl)phenyl]-4-
10 (trifluoromethyl)-4,5-dihydro-1H-imidazole from Step 2
(3.4 g, 7.9 mmol) and *p*-toluenesulfonic acid
monohydrate (700 mg) in toluene (200 mL) was heated to
reflux for 72 hours. The reaction mixture was cooled
and the solvent removed under reduced pressure. The
15 crude residue was redissolved in methylene chloride and
washed with water, aqueous sodium bicarbonate and
brine. After drying (Na_2SO_4), filtration and
concentration *in vacuo*, the crude mixture (3.6 g) was
purified by chromatography on silica gel using
20 toluene/ethyl acetate (8/2) to give pure 2-(3-fluoro-4-
methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-
(trifluoromethyl)-1H-imidazole (2.12 g, 65%) as a white
solid: mp (DSC) 182°C. Anal. Calc'd. for $C_{18}H_{14}N_2SO_3F_4$:
C, 52.17, H, 3.41, N, 6.76, S, 7.74. Found: C, 52.56,
25 H, 3.65, N, 6.53, S, 8.01.

Example 19



2-(4-Chlorophenyl)-4-[(phenylthio)methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

Step 1: Preparation of 1-bromo-3-phenylthio-2-propanone

1-Bromo-3-phenylthio-2-propanone is synthesized by reaction of thiophenol with 2,3-dichloropropene followed by treatment of the resulting product with aqueous NBS as described for Example 15.

Step 2: Preparation of 2-(4-chlorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-[(phenylthio)methyl]-4,5-dihydro-1H-imidazole

To a mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Example 1, Step 1) (1 mmol) and sodium bicarbonate (2 mmol) in acetone (20 mL), 1-bromo-3-phenylthio-2-propanone (1.5 mmol) is added. After heating to reflux for 24 hours, the reaction mixture is filtered, washed with acetone and concentrated in vacuo. The crude product is purified by chromatography (silica gel, toluene/ethyl acetate) to give 2-(4-chlorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-[(phenylthio)methyl]-4,5-dihydro-1H-imidazole.

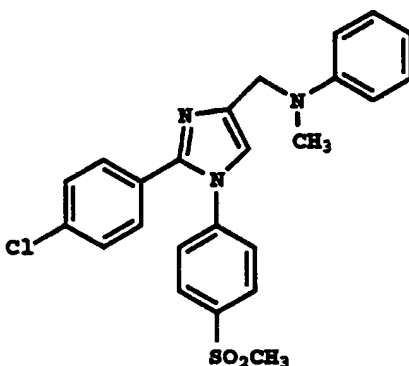
Step 3: Preparation of 2-(4-chlorophenyl)-4-[(phenylthio)methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

A mixture of 2-(4-chlorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-[(phenylthio)methyl]-4,5-dihydro-1H-imidazole (1 mmol) and p-toluenesulfonic acid monohydrate (100 mg) in toluene (70 mL) is heated to reflux for 48 hours. The reaction mixture is cooled and the solvent removed under reduced pressure. The crude residue is redissolved in methylene chloride and washed with water, aqueous sodium bicarbonate and brine. After drying (Na₂SO₄), filtration and concentration in vacuo, the crude mixture is purified

by chromatography on silica gel using hexane/ethyl acetate to give 2-(4-chlorophenyl)-4-[(phenylthio)methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole.

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Example 20



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2-(4-Chlorophenyl)-4-[(N-methyl-N-phenylamino)methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

15

Step 1: Preparation of 1-bromo-3-(N-methyl-N-phenylamine)-2-propanone

1-Bromo-3-(N-methyl-N-phenylamine)-2-propanone is synthesized by reaction of N-methylaniline with 2,3-dichloropropene followed by treatment of the resulting product with aqueous NBS as described for Example 15.

20

Step 2: Preparation of 2-(4-chlorophenyl)-4-hydroxy-4-[(N-methyl-N-phenylamino)methyl]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-imidazole

To a mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Example 1, Step 1) (1 mmol) and sodium bicarbonate (2 mmol) in acetone (20 mL), 1-bromo-3-(N-methyl-N-phenylamine)-2-propanone from Step 1 (1.5 mmol) is added. After heating to reflux for 24 hours, the reaction mixture is filtered, washed with acetone and concentrated in vacuo. The crude product is purified by chromatography

30

(silica gel, toluene/ethyl acetate) to give 2-(4-chlorophenyl)-4-hydroxy-4-[(N-methyl-N-phenylamine)methyl]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-imidazole.

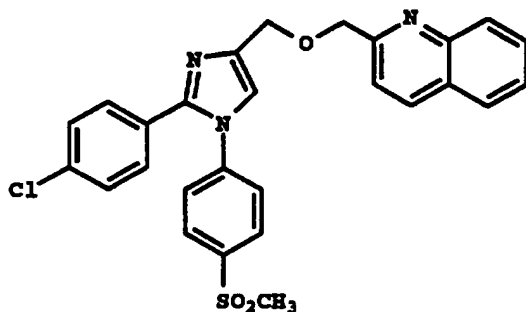
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Step 3: Preparation of 2-(4-chlorophenyl)-4-[(N-methyl-N-phenylamino)methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

A mixture of 2-(4-chlorophenyl)-4-hydroxy-4-[(N-methyl-N-phenylamine)methyl]-1-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1H-imidazole (1 mmol) and *p*-toluenesulfonic acid monohydrate (100 mg) in toluene (70 mL) is heated to reflux for 48 hours. The reaction mixture is cooled and the solvent removed under reduced pressure. The crude residue is redissolved in methylene chloride and washed with water, aqueous sodium bicarbonate and brine. After drying (Na₂SO₄), filtration and concentration *in vacuo*, the crude mixture is purified by chromatography on silica gel using hexane/ethyl acetate to give 2-(4-chlorophenyl)-4-[(N-methyl-N-phenylamine)methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole.

Example 21

25



2-(4-Chlorophenyl)-4-[2-quinolyl)methoxymethyl]-
1-[4-(methylsulfonyl)phenyl]-1H-imidazole

30

Step 1: Preparation of 1-bromo-3-(2-quinolylmethoxy)-2-propanone

The compound 1-bromo-3-(2-quinolylmethoxy)-2-propanone is synthesized by reaction of 2-chloromethylquinoline with 2-chloro-2-propen-1-ol followed by treatment of the resulting quinolyether with aqueous NBS.

Step 2: Preparation of 2-(4-chlorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-[(2-quinolylmethoxy)methyl]-4,5-dihydro-1H-imidazole

To a mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Example 1, Step 1) (1 mmol) and sodium bicarbonate (2 mmol) in acetone (20 mL), 1-bromo-3-(2-quinolylmethoxy)-2-propanone from Step 1 (1.5 mmol) is added. After heating to reflux for 24 hours, the reaction mixture is filtered, washed with acetone and concentrated in vacuo. The crude product is purified by chromatography (silica gel, toluene/ethyl acetate) to give 2-(4-chlorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-[(2-quinolylmethoxy)methyl]-4,5-dihydro-1H-imidazole.

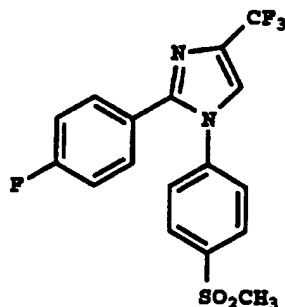
Step 3: Preparation of 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-[(2-quinolylmethoxy)methyl]-4,5-dihydro-1H-imidazole

A mixture of 2-(4-chlorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-[(2-quinolylmethoxy)methyl]-4,5-dihydro-1H-imidazole (1 mmol) and p-toluenesulfonic acid monohydrate (100 mg) in toluene (70 mL) is heated to reflux for 48 hours. The reaction mixture is cooled and the solvent removed under reduced pressure. The crude residue is redissolved in methylene chloride and washed with water, aqueous sodium bicarbonate and brine. After drying (Na₂SO₄), filtration and concentration in vacuo, the crude mixture is purified by chromatography on silica gel using hexane/ethyl acetate to give 2-(4-chlorophenyl)-1-[4-

(methylsulfonyl)phenyl]-4-[(2-quinolylmethoxy)methyl]-1H-imidazole.

Example 22

5



2-(4-Fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole

10

Step 1: Preparation of 4-fluoro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide

To a suspension of 4-(methylsulfonyl)aniline (3.53 g, 20.2 mmol) in toluene (100 mL), trimethylaluminum (15.2 mL, 2M solution in toluene, 30.2 mmol) was added over 15 minutes. The reaction mixture was warmed to room temperature and stirred for 2.5 hours. A solution of 4-fluorobenzonitrile (5 g, 40.3 mmol) in toluene (100 mL) was added over 10 minutes and the reaction mixture heated to 80-85°C. After 20 hours, the reaction mixture was cooled to room temperature and poured over a slurry of silica gel in chloroform. After filtration, the residue was washed with a mixture of methylene chloride/methanol (2/1). The combined filtrates were concentrated in vacuo and the resulting yellowish solid stirred with a mixture of hexane/ether (2/1, 1000 mL). The intermediate was filtered and concentrated. The pale yellow solid 4-fluoro-N-[4-(methylsulfonyl)phenyl] benzenecarboximidamide (5.25 g, 87%) was used in the next reaction without further purification: mp (DSC) 206.2°C. Anal. Calc'd for

$C_{14}H_{13}N_2FSO_3 \cdot 1.25 H_2O$: C, 53.41; H, 4.91; N, 8.90.

Found: C, 53.08; H, 4.50; N, 8.61.

Step 2: Preparation of 2-(4-fluorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-4,5-dihydro-1H-imidazole

To a mixture of 4-fluoro-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Step 1) (4.5 g, 15.4 mmol) and sodium bicarbonate (2.59 g, 30.8 mmol) in isopropanol (200 mL), 3-bromo-1,1,1-trifluoroacetone (3.2 mL) was added. After heating the reaction mixture at 75-80°C for 22 hours, the solvent was removed. The residue was redissolved in methylene chloride and washed with water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude mixture (7.2 g) was purified by chromatography (silica gel, toluene/ethyl acetate, 1/1) to give 2-(4-fluorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-4,5-dihydro-1H-imidazole (3.28 g, 53%) as a white solid: mp (DSC) 203°C. Anal. Calc'd for $C_{17}H_{14}N_2F_4SO_3$: C, 50.75; H, 3.51; N, 6.96. Found: C, 51.16; H, 3.69; N, 6.54.

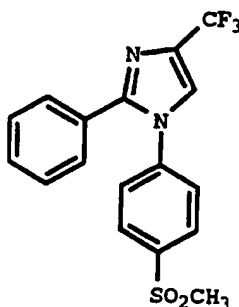
Step 3: Preparation of 2-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole

A mixture of 2-(4-fluorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-4,5-dihydro-1H-imidazole (Step 2) (2.8 g, 7 mmol) and p-toluenesulfonic acid monohydrate (300 mg) in toluene (200 mL) was heated to reflux for 72 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude residue was redissolved in methylene chloride and washed with water, aqueous sodium bicarbonate and brine. After drying (Na_2SO_4), filtration and concentration in vacuo, the crude mixture (3.2 g) was purified by chromatography on silica gel using toluene/ethyl acetate (1/1) to give pure 2-(4-fluorophenyl)-1-[4-

(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole
(1.38 g, 52%) as a white solid: mp (DSC) 205.5°C.

Anal. Calc'd for $C_{17}H_{12}N_2F_4SO_2$: C, 53.13; H, 3.15; N, 7.29; S, 8.34. Found: C, 53.18; H, 3.17; N, 7.26; S, 8.57.

Example 23



1-[4-(Methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole

Step 1: Preparation of N-[4-

(methylsulfonyl)phenyl]benzenecarboximidamide

To a suspension of 4-(methylsulfonyl)aniline (12 g, 70 mmol) in toluene (400 mL), trimethylaluminum (52.5 mL, 2M solution in toluene, 0.1 mol) was added over 15 minutes. The reaction mixture was warmed to room temperature and stirred for 3.5 hours. A solution of benzonitrile (14.5 g, 0.14 mol) in toluene (300 mL) was added over 10 minutes and the reaction mixture heated to 70-75°C. After 17 hours, the reaction mixture was cooled to room temperature and poured over a slurry of silica gel in chloroform. After filtration, the residue is washed with a mixture of methylene chloride/methanol (2/1). The combined filtrates are concentrated in vacuo and the resulting yellowish solid is stirred with a mixture of hexane/ether (2/1, 1000 mL). The intermediate is filtered and washed with more of hexane/ether (2/1). The yellowish solid N-[4-

(methylsulfonyl)phenyl]benzenecarboximidamide (16.7 g, 87%) was used in the next reaction without further purification.

5 Step 2: Preparation of 4-hydroxy-1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-4,5-dihydro-1H-imidazole

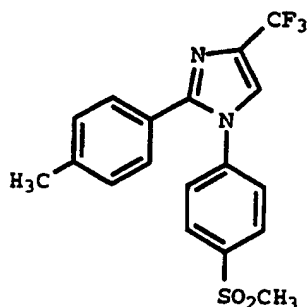
To a mixture of N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Step 1) (16.5 g, 60.1 mmol) and
10 sodium bicarbonate (10.1 g, 0.12 mol) in isopropanol (900 mL), 3-bromo-1,1,1-trifluoroacetone (8.7 mL, 84 mmol) was added. After heating the reaction mixture at 75 -80°C for 20 hours, the solvent was removed. The residue was redissolved in methylene chloride and
15 washed with water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude mixture was purified by chromatography (silica gel, hexane/ethyl acetate, 45/55) to give 4-hydroxy-1-[4-(methylsulfonyl)phenyl]-
20 2-phenyl-4-trifluoromethyl-4,5-dihydro-1H-imidazole (13.6 g, 59%) as a white solid: mp 189 - 190°C. Anal. Calc'd for C₁₇H₁₅N₂F₃SO₃: C, 53.12; H, 3.93; N, 7.29; S, 8.34. Found: C, 53.05; H, 3.90; N, 7.14; S, 8.38.

25 Step 3: Preparation of 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole

A mixture of 4-hydroxy-1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-4,5-dihydro-1H-imidazole (Step 2) (5.43 g, 14.1 mmol) and
30 p-toluenesulfonic acid monohydrate (1.63 g) in toluene (500 mL) was heated to reflux for 96 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude residue was redissolved in methylene chloride and washed with
35 water, aqueous sodium bicarbonate and brine. After drying (Na₂SO₄), filtration and concentration in vacuo, the crude mixture was purified by chromatography on silica gel using hexane/ethyl acetate (65/35) to give

pure 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole (3.12 g, 60%) as a white solid: mp (DSC) 233°C. Anal. Calc'd for C₁₇H₁₃N₂F₃SO₂: C, 55.73; H, 3.58; N, 7.65; S, 8.75. Found: C, 55.49; H, 3.47; N, 7.46; S, 8.95.

Example 24



2-(4-Methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole

Step 1: Preparation of 4-methyl-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide

To a suspension of 4-(methylsulfonyl)aniline (3.57 g, 20.9 mmol) in toluene (150 mL), trimethylaluminum (15.6 mL, 2M solution in toluene, 31.4 mmol) was added over 15 minutes. The reaction mixture was warmed to room temperature and stirred for 2.5 hours. A solution of 4-methylbenzonitrile (5 mL, 41.8 mmol) in toluene (100 mL) was added over 10 minutes and the reaction mixture heated to 80-85°C. After 20 hours, the reaction mixture was cooled to room temperature and poured over a slurry of silica gel in chloroform. After filtration, the residue was washed with a mixture of methylene chloride/methanol (2/1). The combined filtrates are concentrated in vacuo and the resulting yellowish solid was stirred with a mixture of hexane/ether (2/1, 600 mL). The intermediate was filtered and washed with more of hexane/ether (2/1).

The pale yellow solid 4-methyl-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (5.3 g, 88%) was used in the next reaction without further purification: mp (DSC) 213°C. Anal. Calc'd for C₁₅H₁₆N₂SO₂: C, 62.48; H, 5.59; N, 9.71. Found: C, 62.00, H, 5.52; N, 9.60.

10 Step 2: Preparation of 2-(4-methylphenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-4,5-dihydro-1H-imidazole

To a mixture of 4-methyl-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (Step 1) (5 g, 17.4 mmol) and sodium bicarbonate (2.9 g, 34.7 mmol) in isopropanol (200 mL), 3-bromo-1,1,1-trifluoroacetone (3.6 mL, 34.7 mmol) was added. After heating the reaction mixture at 75-80°C for 20 hours, the solvent was removed. The residue was redissolved in methylene chloride and washed with water. The organic fractions were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude mixture (8.9 g) was purified by chromatography (silica gel, toluene/ethyl acetate 6/4) to give 2-(4-methylphenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-4,5-dihydro-1H-imidazole (3.28 g, 47%) as a white solid: mp 198 - 199°C. Anal. Calc'd for C₁₈H₁₇N₂F₃SO₃ • 0.3 PhMe C, 56.67; H, 4.59; N, 6.58. Found: C, 56.95; H, 4.68; N, 6.13.

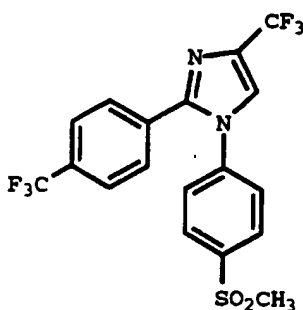
30 Step 3: Preparation of 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole

A mixture of 2-(4-methylphenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-4,5-dihydro-1H-imidazole (Step 2) (0.9 g, 2.3 mmol) and p-toluenesulfonic acid monohydrate (150 mg) in toluene (100 mL) was heated to reflux for 72 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude residue was redissolved in methylene chloride and washed with

water, aqueous sodium bicarbonate and brine. After drying (Na₂SO₄), filtration and concentration *in vacuo*, the crude mixture was purified by chromatography on silica gel using toluene/ethyl acetate (1/1) to give
5 pure 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (462 mg, 54%) as a white solid: mp (DSC) 190°C. Anal. Calc'd for C₁₈H₁₅N₂F₃SO₂: C, 56.84; H, 3.97; N, 7.36; S, 8.43. Found: C, 56.66; H, 3.82; N, 7.23; S, 8.45.

10

Example 25



15

1-[4-(Methylsulfonyl)phenyl]-2-(4-trifluoromethylphenyl)-4-trifluoromethyl-1H-imidazole

Step 1: Preparation of 4-(trifluoromethyl)-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide
20

To a suspension of 4-(methylsulfonyl)aniline (10 mmol) in toluene (100 mL), trimethylaluminum (2M solution in toluene, 15 mmol) is added over 15 minutes. The reaction mixture is warmed to room temperature and stirred for 2.5 hours. A solution of 4-
25 trifluoromethylbenzonitrile (20 mmol) in toluene (50 mL) is added over 10 minutes and the reaction mixture is heated to 80-85°C. After 20 hours, the reaction mixture is cooled to room temperature and poured over a
30 slurry of silica gel in chloroform. After filtration, the residue is washed with a mixture of methylene chloride/methanol (2/1). The combined filtrates are

concentrated in vacuo and the resulting yellowish solid is stirred with a mixture of hexane/ether (2/1, 1000 mL). The intermediate is filtered and washed with more of hexane/ether (2/1). The pale yellow solid 4-(trifluoromethyl)-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide is used in the next reaction without further purification.

Step 2: Preparation of 4-hydroxy-1-[4-(methylsulfonyl)phenyl]-2-(4-trifluoromethylphenyl)-4-trifluoromethyl-4,5-dihydro-1H-imidazole

To a mixture of 4-(trifluoromethyl)-N-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (10 mmol) and sodium bicarbonate (20 mmol) in isopropanol (100 mL), 3-bromo-1,1,1-trifluoroacetone (20 mmol) is added. After heating the reaction mixture at 70-75°C for 20 hours, the solvent is removed. The residue is redissolved in methylene chloride and washed with water. The organic fractions are combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product is purified by chromatography (silica gel, toluene/ethyl acetate, 7/3) to give 4-hydroxy-1-[4-(methylsulfonyl)phenyl]-2-(4-trifluoromethylphenyl)-4-trifluoromethyl-4,5-dihydro-1H-imidazole.

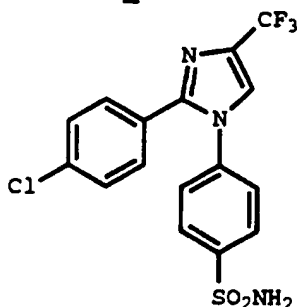
Step 3: Preparation of 1-[4-(methylsulfonyl)phenyl]-2-(4-trifluoromethylphenyl)-4-trifluoromethyl-1H-imidazole

A mixture of 4-hydroxy-1-[4-(methylsulfonyl)phenyl]-2-(4-trifluoromethylphenyl)-4-trifluoromethyl-4,5-dihydro-1H-imidazole (10 mmol) and p-toluenesulfonic acid monohydrate (1 mmol) in toluene (100 mL) is heated to reflux for 72 hours. The reaction mixture is cooled and the solvent removed under reduced pressure. The crude residue is redissolved in methylene chloride and washed with water, aqueous sodium bicarbonate and brine. After drying (Na₂SO₄), filtration and concentration in vacuo, the crude

mixture is purified by chromatography on silica gel using toluene/ethyl acetate to give pure 1-[4-(methylsulfonyl)phenyl]-2-(4-trifluoromethylphenyl)-4-trifluoromethyl-1H-imidazole.

5

Example 26

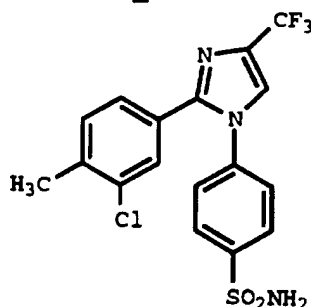


4-[2-(4-Chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide

10 To a clear solution of 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole from Example 2 (400 mg, 1 mmol) in tetrahydrofuran (THF) (8 mL) at 0°C, *n*-BuMgCl (2M solution in THF, 2 mL, 4 mmol) was added over 10
15 minutes. After stirring for additional 10 minutes, ice bath was removed and solution stirred for 1 hour. The reaction mixture was re-cooled to 0°C and triethylborane (1M solution in THF, 5 mL, 5 mmol) was added. After stirring for 2 hours, the reaction was
20 heated to reflux for 48 hours. The reaction mixture was cooled to room temperature and treated with aqueous sodium acetate (1 g in 4 mL water). After stirring for 5 minutes, solid hydroxylamine-O-sulfonic acid (1 g) was added and the mixture stirred for 20 hours. The
25 reaction mixture was diluted with water and extracted with ether (2x250). The ethereal layer was dried over sodium sulfate, filtered and concentrated in vacuo. The crude solid (568 mg) was purified by chromatography [silica gel, ethyl acetate/toluene (3/7)] to give 4-[2-(4-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (260 mg, 65%): mp (DSC) 225°C.
30 Anal. Calc'd. for C₁₆H₁₁N₃SO₂F₃Cl: C, 47.83, H, 2.76 N,

10.46, S, 7.98. Found: C, 48.00, H, 2.83, N, 10.14, S, 7.94.

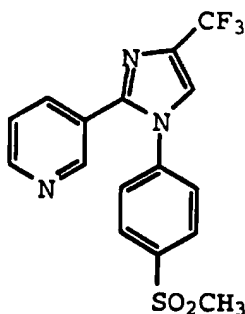
Example 27



5

4-[2-(3-Chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide

To a clear solution of 2-(3-chloro-4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (Example 16) (500 mg, 1.2 mmol) in tetrahydrofuran (10 mL) at 0°C, *n*-BuMgCl (2M solution in THF, 2.4 mL, 4.8 mmol) was added over 10 minutes. After stirring for additional 10 minutes, ice bath was removed and solution stirred for 1 hour. The reaction mixture was re-cooled to 0°C and triethylborane (1M solution in THF, 6 mL, 6 mmol) was added. After stirring for 2 hours, the reaction was heated to reflux for 72 hours. The reaction mixture was cooled to room temperature and treated with aqueous sodium acetate (1 g in 4 mL water). After stirring for 5 minutes, solid hydroxylamine-O-sulfonic acid (1 g) was added and the mixture stirred for 20 hours. The reaction mixture was diluted with water and extracted with ether (2x250). The ethereal layer was dried over sodium sulfate, filtered and concentrated in vacuo. The crude product (710 mg) was purified by chromatography (silica gel, ethyl acetate/toluene 3/7) to give pure 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (180 mg, 36%) as a white solid: mp(DSC) 222°C. Anal. Calc'd. for C₁₇H₁₃N₃SO₂F₃Cl: C, 49.10, H, 3.15, N, 10.11. Found: C, 49.42, H, 3.19, N, 9.75.

Example 28

5 **3-[1-[4-(Methylsulfonyl)phenyl]-4-trifluoromethyl-
1H-imidazol-2-yl]pyridine**

Step 1: Preparation of N-[4-(methylsulfonyl)phenyl]-
-3-pyridinecarboximidamide

10 To a suspension of 4-(methylsulfonyl)aniline
hydrochloride (6 g, 28.8 mmol) in toluene (150 ml) at 0 °C,
trimethylaluminum (2M solution in toluene, 21.6 ml, 43.2
mmol) was added over 15 minutes. The reaction mixture was
warmed to room temperature and stirred for 2.5 hours. A
15 solution of 3-cyanopyridine (6 g, 57.6 mmol) in toluene
(150 ml) was added over 10 minutes and the reaction mixture
was heated to 90-95°C. After 24 hours, the reaction mixture
was cooled to room temperature and poured over a slurry of
silica gel in chloroform. After filtration, the residue was
20 washed with a mixture of methylene chloride/methanol and
later methanol. The combined filtrates were concentrated
and the resulting yellowish solid was stirred with ethyl
acetate (1000 ml) and filtered. The pale yellow amidine
(4.5 g, 34%) was used in the next reaction without further
25 purification: mp (DSC) 265°C. Anal Calc'd. for
C₁₃H₁₄N₃SO₂Cl·0.5 H₂O: C, 48.67, H, 4.71, N, 13.10. Found:
C, 48.34, H, 4.26, N, 12.77.

30 Step 2: Preparation of 3-[4-hydroxy-1-[4-
(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-
imidazol-2-yl]pyridine

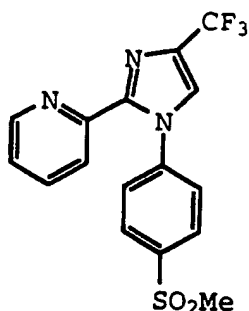
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To a mixture of the amidine of Step 1 (4.4 g, 16 mmol) and sodium bicarbonate (2.68 g, 32 mmol) in isopropanol (400 ml), 3-bromo-1,1,1-trifluoroacetone (2.5 ml, 24 mmol) was added. After heating at 60-65°C for 36 hours, the reaction mixture was cooled and filtered. The residue was washed with methylene chloride and the combined organic fractions were dried over sodium sulfate, filtered and concentrated. The crude mixture (16.2 g) was purified by chromatography [silica gel, ethyl acetate/acetone (98:2)] to give the compound (3.7 g, 60%) as a white solid. Anal Calc'd. for $C_{16}H_{14}N_3SO_3F_3 \cdot 0.5 H_2O$: C, 48.18, H, 3.92, N, 10.53. Found: C, 48.52, H, 3.61, N, 9.79.

Step 3: Preparation of 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

A mixture of the compound of step 2 (3.6 g, 9.35 mmol) and p-toluenesulfonic acid monohydrate (0.52 g, 2.7 mmol) in toluene (280 ml) was heated to reflux for 24 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude mixture was purified by chromatography on silica gel using ethyl acetate/acetone (98/2) to give pure 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (790 mg, 23%) as a white solid: mp (DSC) 193°C. Anal Calc'd. for $C_{16}H_{12}N_3SO_2F_3$: C, 52.30, H, 3.29, N, 11.44, S, 8.73. Found: C, 52.38, H, 3.26, N, 11.30, S, 8.76.

Example 29



5 2-[1-[4-(Methylsulfonyl)phenyl]-4-trifluoromethyl-
1H-imidazol-2-yl]pyridine

Step 1: Preparation of N-[4-(methylsulfonyl)phenyl]-2-pyridinecarboximidamide

10 To a suspension of 4-(methylsulfonyl)aniline
hydrochloride (6 g, 28.8 mmol) in toluene (150 ml) at 0°C,
trimethylaluminum (2M solution in toluene, 21.6 ml, 43.2
mmol) was added over 15 minutes. The reaction mixture was
warmed to room temperature and stirred for 2.5 hours. A
15 solution of 2-cyanopyridine (6 g, 57.6 mmol) in toluene
(150 ml) was added over 10 minutes and the reaction mixture
was heated to 85-90°C. After 24 hours, the reaction mixture
was cooled to room temperature and poured over a slurry of
silica gel in chloroform. After filtration, the residue was
20 washed with a mixture of methylene chloride/methanol and
later methanol. The combined filtrates were concentrated
and the resulting yellowish solid was stirred with ethyl
acetate (1500 ml) and filtered. The pale yellow solid (5.2
g, 66%) was used in the next reaction without further
25 purification.

Step 2: Preparation of 2-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine

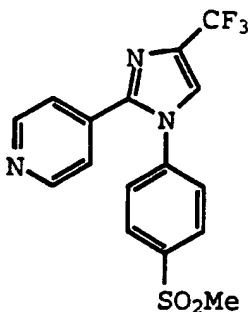
30 To a mixture of the amidine of step 1 (4.4 g, 16
mmol) and sodium bicarbonate (2.7 g, 32 mmol) in

isopropanol (400 ml), 3-bromo-1,1,1-trifluoroacetone (2.5 ml, 24 mmol) was added. After heating at 75-80°C for 24 hours, the reaction mixture was cooled and filtered. The residue was washed with methylene chloride and the combined
5 organic fractions were dried over sodium sulfate, filtered and concentrated. The crude product (16.2 g) was purified by chromatography (silica gel, ethyl acetate/toluene 1/1) to give 2-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine
10 (1.1 g, 18%) as a white solid: mp 195-198°C. Anal. Calc'd. for C₁₆H₁₄N₃SO₃F₃ : C, 49.87, H, 3.66, N, 10.90. Found: C, 50.13, H, 3.66, N, 10.30.

Step 3: Preparation of 2-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine
15

A mixture of 2-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine from step 2 (1.0 g, 2.6 mmol) and p-toluenesulfonic acid monohydrate (0.2 g, 2.7 mmol) in
20 toluene (100 ml) was heated to reflux for 24 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude mixture (1.2 g) was purified by chromatography on silica gel using ethyl acetate/toluene (1/1) to give pure 2-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (620 mg, 65%) as
25 a white solid: mp (DSC) 184°C. Anal. Calc'd. for C₁₆H₁₂N₃SO₂F₃ : C, 52.30, H, 3.29, N, 11.44. Found: C, 52.23, H, 3.23, N, 11.19.

Example 30



5 **4-[1-[4-(Methylsulfonyl)phenyl]-4-trifluoromethyl-
1H-imidazol-2-yl]pyridine**

Step 1: Preparation of N-[4-(methylsulfonyl)
phenyl]-4-pyridinecarboximidamide

10 To a suspension of 4-(methylsulfonyl)aniline
hydrochloride (10 g, 48.1 mmol) in toluene (250 ml) at 0°C,
trimethylaluminum (2M solution in toluene, 36.1 ml, 72.2
mmol) was added over 10 minutes. The reaction mixture was
warmed to room temperature and stirred for 2.5 hours. A
15 solution of 4-cyanopyridine (10 g, 96.2 mmol) in toluene
(250 ml) was added over 10 minutes and the mixture was
heated to 70°C. After 24 hours, the reaction mixture was
cooled to room temperature and poured over a slurry of
silica gel in chloroform. After filtration, the residue
20 was washed with a mixture of methylene chloride/methanol
and later with methanol. The combined filtrates were
concentrated and the resulting yellowish solid was stirred
with ethyl acetate and filtered. The pale yellow solid (4.8
g, 36%) was used in the next reaction without further
25 purification. Anal. Calc'd. for C₁₃H₁₄N₃SO₂ H₂O: C,
47.34, H, 4.89, N, 12.74, S, 9.72. Found: C, 47.69, H,
4.35, N, 12.77, S, 9.74.

Step 2: Preparation of 4-[4-hydroxy-1-[4-(methylsulfonyl)
30 phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-
yl]pyridine

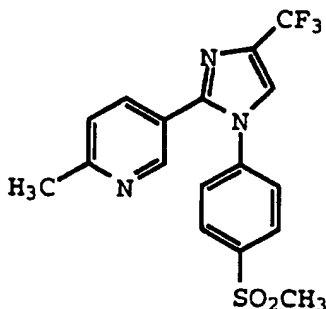
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To a mixture of the amidine of step 1 (4.75 g, 16 mmol) and sodium bicarbonate (2.86 g, 34.4 mmol) in isopropanol (400 ml), 3-bromo-1,1,1-trifluoroacetone (2.7 ml, 26 mmol) was added. After heating at 75-80°C for 24 hours, the reaction mixture was cooled and filtered. The residue was washed with methylene chloride and the combined organic fractions were dried over sodium sulfate, filtered and concentrated. The crude product (16.2 g) was purified by chromatography (silica gel, ethyl acetate/isopropanol (95/5)) to give 4-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine (1.55 g, 23%) as a white solid: mp 219 °C, Anal. Calc'd. for C₁₆H₁₄N₃SO₃F₃ C, 49.87, H, 3.66, N, 10.90, S, 8.32. Found: C, 49.93, H, 3.51, N, 10.79, S, 8.66.

Step 3: Preparation of 4-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

A mixture of the 4,5-dihydro-imidazole of step 2 (0.85 g, 2.2 mmol) and *p*-toluenesulfonic acid monohydrate (0.12 g) in toluene (150 ml) was heated to reflux for 24 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude mixture was purified by chromatography on silica gel using ethyl acetate/acetone (96/4) to give pure 4-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (330 mg, 41%) as a white solid: mp (DSC) 197 °C. Anal. Calc'd. for C₁₆H₁₂N₃SO₂F₃ : C, 52.30, H, 3.29, N, 11.44, S, 8.73. Found: C, 52.19, H, 3.26, N, 11.25, S, 8.99.

Example 31



2-Methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

Step 1: Preparation of 2-methyl-N-[4-

5 (methylsulfonyl)phenyl]-5-pyridinecarboximidamide

To a suspension of 4-(methylsulfonyl)aniline hydrochloride (8.8 g, 42.3 mmol) in toluene (150 ml) at 0°C, trimethylaluminum (2M solution in toluene, 42.3 ml, 84.6 mmol) was added over 10 minutes. The reaction mixture
10 was warmed to room temperature and stirred for 2.5 hours. A solution of 6-methyl-4-cyanopyridine (10 g, 84.6 mmol) in toluene (150 ml) was added over 10 minutes and the mixture was heated to 80-85°C. After 24 hours, the reaction mixture was cooled to room temperature and poured over a slurry of
15 silica gel in chloroform. After filtration, the residue was washed with a mixture of methylene chloride/methanol and later with methanol. The combined filtrates were concentrated and the resulting yellowish solid was stirred with ethyl acetate and filtered. The pale yellow solid (9.8
20 g, 80%) was used in the next reaction without further purification. Anal Calc'd. for C₁₄H₁₅N₃SO₂·H₂O: C, 54.71, H, 5.57, N, 13.67. Found: C, 54.62, H, 5.24, N, 13.67.

Step 2: Preparation of 2-methyl-5-[4-hydroxy-1-[4-

25 (methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine

To a mixture of the amidine of Step 1 (9.8 g, 33.9 mmol) and sodium bicarbonate (5.7 g, 67.8 mmol) in isopropanol (700 ml), 3-bromo-1,1,1-trifluoroacetone (5.3
30 ml, 50.8 mmol) was added. After heating at 80-85°C for 24 hours, the reaction mixture was cooled and filtered. The residue was washed with methylene chloride and the combined organic fractions were dried over sodium sulfate, filtered and concentrated. The crude material (25.7 g) was purified
35 by chromatography (silica gel, ethyl acetate/acetone, 98/2) to give 2-methyl-5-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine

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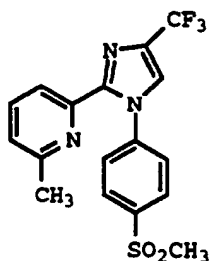
(6.3 g, 46%) as a white solid: Anal. Calc'd. for $C_{17}H_{16}N_3SO_3F_3$: C, 50.55, H, 4.12, N, 10.40. Found: C, 50.51, H, 3.91, N, 10.25.

5 Step 3: Preparation of 2-methyl-5-[1-[4-(methanesulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

A mixture of the 4,5-dihydro-imidazole of step 2 (6.2 g, 15.5 mmol) and *p*-toluenesulfonic acid monohydrate (1.6 g, 8.4 mmol) in toluene (550 ml) was heated to reflux for 24 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude mixture (8.2 g) was purified by chromatography on silica gel using ethyl acetate/acetone (98/2) to give pure 2-methyl-5-[1-[4-(methanesulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (3.9 g, 66%) as a white solid: mp (DSC) 163°C. Anal Calc'd. for $C_{17}H_{14}N_3SO_2F_3$: C, 53.54, H, 3.70, N, 11.02, S, 8.41. Found: C, 53.12, H, 3.56, N, 11.00, S, 8.50.

20

Example 32



25 2-Methyl-6-[1-[4-(methanesulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

Step 1: Preparation of 2-methyl-N-[4-(methanesulfonyl)phenyl]-6-pyridinecarboximidamide

30 To a suspension of 4-(methanesulfonyl)aniline hydrochloride (4.2 g, 20.3 mmol) in toluene (100 ml) at 0°C, was added trimethylaluminum (2M solution in toluene, 12 ml, 24 mmol) over 10 minutes. The

reaction mixture was warmed to room temperature and stirred for 2 hours. A solution of 6-methyl-2-cyanopyridine (3.6 g, 30.5 mmol) in toluene (100 ml) was added over 10 minutes and the mixture was heated to 85-90°C. After 24 hours, the reaction mixture was cooled to room temperature and poured over a slurry of silica gel in chloroform. After filtration, the residue was washed with a mixture of methylene chloride/methanol and later with methanol. The combined filtrates were concentrated and the resulting yellowish solid was stirred with hexane and ethyl acetate (1000 ml) and filtered. The white solid (5.1 g, 87%) was used in the next reaction without further purification. Anal. Calc'd. for $C_{14}H_{16}N_3SClO_2 \cdot 0.2H_2O$: C, 51.05, H, 5.02, N, 12.76. Found: C, 50.97, H, 4.78, N, 12.80.

Step 2: Preparation of 2-methyl-6-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine

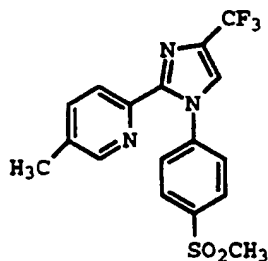
To a mixture of the amidine of Step 1 (4.9 g, 16.95 mmol) and sodium bicarbonate (2.85 g, 33.9 mmol) in isopropanol (300 ml), 3-bromo-1,1,1-trifluoroacetone (2.65 ml, 25.4 mmol) was added. After heating at 80-85°C for 24 hours, the reaction mixture was cooled and filtered. The residue was washed with methylene chloride and the combined organic fractions were dried over sodium sulfate, filtered and concentrated. The crude mixture (9 g) was purified by chromatography (silica gel, ethyl acetate/isopropanol/ammonium hydroxide 95/5/0.5) to give 2-methyl-6-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine (1.4 g, 21%) as a white solid: Anal. Calc'd. for $C_{17}H_{16}N_3SO_3F_3$: C, 51.12, H, 4.02, N, 10.52. Found: C, 51.43, H, 3.96, N, 10.06.

Step 3: Preparation of 2-methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

5 A mixture of the 4,5-dihydro-imidazole of step 2 (1.3 g, 3.26 mmol) and *p*-toluenesulfonic acid monohydrate (0.26 g, 1.36 mmol) in toluene (200 ml) was heated to reflux for 24 hours. The reaction mixture was cooled and the solvent removed under
10 reduced pressure. The crude mixture (1.56 g) was purified by chromatography on silica gel using ethyl acetate/acetone (98/2) to give pure 2-methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (0.48 g, 38%) as a white
15 solid: mp (DSC) 205°C. Anal. Calc'd. for $C_{17}H_{14}N_3SO_2F_3 \cdot 0.25H_2O$: C, 52.91, H, 3.79, N, 10.89, S, 8.31. Found: C, 52.67, H, 3.55, N, 10.64, S, 8.68.

20

Example 33



25 **5-Methyl-2-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine**

Step 1: Preparation of 5-methyl-2-cyanopyridine

To a solution of 2-fluoro-5-methylpyridine (39 g; 351.5 mmol) in 141 ml of dimethylsulfoxide was added 17.23
30 g of sodium cyanide (351.5 mmol). After stirring for 3 days at 150°C, an additional 3 g of sodium cyanide was added and heating was continued for 5 hours. The reaction

mixture was cooled to 25°C then poured into 525 ml of ice water. The solution was filtered through a coarse fritted funnel and a dark brown solid was collected. The solid was air dried to give 17 g of the desired cyanopyridine: Anal
5 Calc'd. for C₇H₆N₂: C, 71.17; H, 5.12; N, 23.71. Found: C, 69.91; H, 5.24; N, 23.26.

Step 2: Preparation of 5-methyl-N-[4-(methylthio)phenyl]-2-pyridinecarboximidamide

10 To a solution of 4-thiomethylaniline (8.25 g; 59 mmol) in 1,2-dichloroethane (164 ml) at 0°C, triethylaluminum (1.9M solution in toluene, 31.2 ml, 59 mmol) was added over 10 minutes. The reaction mixture was warmed to room temperature and stirred for 1.5 hours. A solution of 5-
15 methyl-2-cyanopyridine (Step 1) (59 mmol) in 1,2-dichloroethane (62 ml) was added over 10 minutes and the mixture was heated to reflux. After 12 hours, the reaction mixture was cooled to room temperature and 50 g of silica gel were added. The suspension was stirred for 1-2 hours
20 at 25°C and 12 ml of methanol was added and stirred at 25°C. After filtration through Celite®, the residue was washed with a mixture of methylene chloride/methanol and later with methanol. The combined filtrates were concentrated and the resulting solid stirred with
25 hexane/ethyl acetate (1000 ml) and filtered. The solid obtained (7g) was used in the next reaction without further purification: Anal Calc'd. for C₁₄H₁₅N₃•0.3 H₂O: C, 63.99; H, 5.98; N, 15.99. Found: C, 64.05; H, 6.06; N, 16.11.

30

Step 3: Preparation of 5-methyl-2-[4-hydroxy-1-[4-(methylthio)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine

To a mixture of the amidine of step 2 (10 g, 52.41
35 mmol) and sodium bicarbonate (8.6 g, 103 mmol) in isopropanol (1200 ml), 3-bromo-1,1,1-trifluoroacetone (10 g, 52 mmol) was added. After heating at reflux for 22

hours, the reaction mixture was cooled and filtered. The residue was dissolved in methylene chloride and washed water than brine. The organic extracts were dried (MgSO₄), filtered and concentrated. The crude mixture was purified
5 by chromatography (silica gel, 100% ethyl acetate) to give the desired dihydro-imidazole (5.1 g): Anal Calc'd. for C₁₇H₁₆N₃SOF₃: C, 55.58; H, 4.39; N, 11.44. Found: C, 55.54; H, 4.35; N, 11.20.

10 Step 4: Preparation of 5-methyl-2-[1-[4-(methylthio)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

A mixture of the dihydro-imidazole of step 3 (3.95 g, 13.9 mmol) and *p*-toluenesulfonic acid monohydrate (785 mg, 4 mmol) in toluene (500 ml) was heated to reflux for 4-5
15 hours. The reaction mixture was cooled and 10 ml of triethylamine was added and the solvent removed under reduced pressure. The crude mixture was purified by chromatography on silica gel using ethyl acetate to give
20 the desired product which was used in the next reaction without further purification.

25 Step 5: Preparation of 5-methyl-2-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

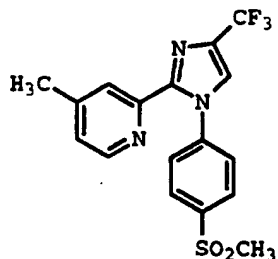
To solution of the methylthio compound from step 4 (3.95 g, 11.5 mmol) in 45 ml of methanol was added an aqueous solution of Oxone[®] (6.94 g dissolved in 28 ml of water). After stirring at 25°C for 4-5 hours, the solvent
30 was removed under reduced pressure, redissolved in 50 ml of methylene chloride and extracted with 50 ml of an aqueous solution of sodium bicarbonate. The organic extracts were dried (MgSO₄), filtered and concentrated. The crude material was purified by chromatography (silica gel; 50%
35 ethyl acetate/ toluene) to provide 1.6 g of the desired product: mp 196°C. Anal Calc'd. for C₁₇H₁₄N₃SO₂F₃: C,

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53.54; H, 3.70; N, 11.02; S, 8.41. Found: C, 53.09; H, 3.43; N, 10.75; S, 8.69.

Example 34

5



4-Methyl-2-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

10

Step 1: Preparation of 2-cyano-4-methylpyridine

To a suspension of 4-picoline N-oxide (13.64 g, 0.124 mole) in 82 ml of THF, under an inert atmosphere, was added trimethylsilyl cyanide (20.1 ml, 0.15 mole) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (4.4 ml, 0.028 mole). After stirring at 25 °C for 12 hours, the reaction mixture was heated to reflux. After 4.5 hours, the solvent was removed under reduced pressure and the crude sample was eluted with methylene chloride through a pad of Florisil®. The solvent was removed under reduced pressure to provide (8.7 g, 60%) of 2-cyano-4-methyl pyridine, a white crystalline solid: mp 88-89 °C Anal. Calc'd. for C₇H₆N₂: C, 71.17; H, 5.12; N, 23.71. Found: C, 70.17; H, 5.12; N, 23.44.

25

Step 2: Preparation of 4-methyl-N-[4-(methylsulfonyl)phenyl]-2-pyridinecarboximidamide

To a solution of 4-methylsulfonyl aniline (7.62 g, 44.5 mmol) in 40 ml of 1,2-dichloroethane, was added 23.4 ml of a 1.9 M solution of triethylaluminum in toluene. After stirring for 1.5 hours at 0 °C, 2-cyano-4-methyl-pyridine from step 1 (5.26 g, 44.5 mmol)

30

was added. The reaction mixture was heated to reflux for 20 hours and poured onto a pad of silica gel, in a fritted filter funnel, pre-wetted and washed with 50% methanol/methylene chloride. The filtrates were
5 evaporated under reduced pressure to provide 11.05 g (85%) of the desired amidine as a light brown solid: mp 180-184°C Anal. Calc'd.. for C₁₄H₁₅N₃O₂S: C, 58.11; H, 5.23; N, 14.52. Found: C, 57.56; H, 5.15; N, 14.35.

10

Step 3: Preparation of 4-methyl-2-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine

To the amidine of step 2 (12.9 g, 44.67 mmol) and
15 sodium bicarbonate (7.15 g, 85.1 mmol) in 1L of isopropanol, 3-bromo-1,1,1-trifluoro-acetone (12.3 g, 64.4 mmol) was added. The mixture was heated to reflux. After 24 hours, the solvent was removed under reduced pressure and the resulting residue was partitioned
20 between methylene chloride and brine. The organic extracts were dried (MgSO₄), filtered and the solvent was removed under reduced pressure to provide a dark brown oil which was purified by flash chromatography (SiO₂, 5% isopropanol/methylene chloride) to provide
25 3.81 g (24%) of the 4,5-dihydro-imidazole as a brown solid.

Step 4: Preparation of 4-methyl-2-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

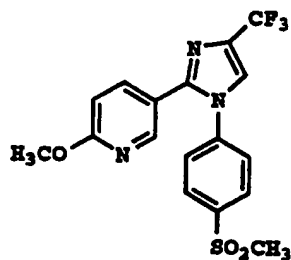
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To a suspension of the 4,5-dihydro-imidazole of step 3 (3.82 g, 10.78 mmol) in 700 ml of toluene was added 0.62 g of *p*-toluenesulfonic acid. After heating at reflux for 12 hours, an additional 0.3 g of *p*-
35 toluenesulfonic acid was added. After 12 hours, 2.7 ml of triethylamine was added and the solvent was removed under reduced pressure to provide 5.17 g of crude

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compound. Crude compound was purified by chromatography twice (SiO₂; 30% heptane/ethyl acetate) by HPLC to provide 263 mg of the targeted compound. Impure fractions containing the desired product were recombined and repurified by chromatography using HPLC (SiO₂; 50% ethyl acetate/toluene) to provide an additional 639.5 mg of the desired compound: mp (DSC) 195 °C. Anal. Calc'd. for C₁₇H₁₄F₃N₃O₂S: C, 53.54; H, 3.70; N, 11.02; S, 8.41. Found: C, 53.21; H, 3.71; N, 10.77; S, 8.63.

Example 35



2-Methoxy-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

Step 1: Preparation of 2-methoxy-N-[4-

(methylsulfonyl)phenyl]-5-pyridinecarboximidamide

To a suspension of 4-(methylsulfonyl)aniline hydrochloride (1.8 g, 8.7 mmol) in toluene (50 ml) at 0°C, trimethylaluminum (2M solution in toluene, 5.2 ml, 10.4 mmol) was added over 10 minutes. The reaction mixture was warmed to room temperature and stirred for 2 hours. A solution of 6-methoxy-3-cyanopyridine (1.75 g, 13 mmol) in toluene (100 ml) was added over 10 minutes and the mixture was heated to 85-90°C. After 24 hours, the reaction mixture was cooled to room temperature and poured over a slurry of silica gel in chloroform. After filtration, the residue was washed with a mixture of

methylene chloride and methanol and later with methanol. The combined filtrates were concentrated and the resulting yellowish solid was stirred with ethyl acetate (1000 ml) and filtered. The white
5 solid (2 g, 75%) was used in the next reaction without further purification. Anal. Calc'd. for $C_{14}H_{16}N_3SClO_3 \cdot 0.5 H_2O$: C, 47.93, H, 4.88, N, 11.98. Found: C, 48.01, H, 4.82, N, 11.32.

10 Step 2: Preparation of 2-methoxy-5-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine

To a mixture of the amidine of step 1 (1.9 g, 6.23 mmol) and sodium bicarbonate (1.05 g, 12.46
15 mmol) in isopropanol (150 ml), 3-bromo-1,1,1-trifluoroacetone (0.97 ml, 9.34 mmol) was added. After heating at 85-90°C for 48 hours, the reaction mixture was cooled and filtered. The residue was washed with methylene chloride and the combined
20 organic fractions were dried over sodium sulfate, filtered and concentrated. The crude mixture (4.25 g) was purified by chromatography (silica gel, methylene chloride/methanol/ammonium hydroxide, 95/5/0.5) to give the 4,5-dihydro-imidazole (1.1 g,
25 42%) as a white solid: Anal. Calc'd. for $C_{17}H_{16}N_3SO_4F_3 \cdot 0.5 EtOAc$: C, 49.67, H, 4.39, N, 9.15. Found: C, 49.80, H, 4.06, N, 9.33.

30 Step 3: Preparation of 2-methoxy-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

A mixture of the 4,5-dihydro-imidazole of step 2 (0.8 g, 1.93 mmol) and *p*-toluenesulfonic acid monohydrate (0.2 g, 1.04 mmol) in toluene (150 ml)
35 was heated to reflux for 24 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude mixture (1.1 g) was

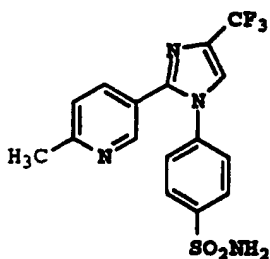
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purified by chromatography on silica gel using ethyl acetate/toluene (1/1) to give pure 2-methoxy-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (0.38 g, 49%) as a white

5 solid: mp (DSC) 166°C. Anal. Calc'd. for $C_{17}H_{14}N_3SO_3F_3$: C, 51.38, H, 3.55, N, 10.57. Found: C, 51.38, H, 3.25, N, 10.41.

Example 36

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4-[2-(6-Methylpyridin-3-yl)-4-
(trifluoromethyl)-1H-imidazol-1-
15 yl]benzenesulfonamide

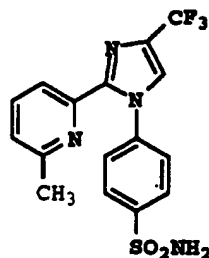
To a clear solution of Example 31 (2.4 g, 6.3 mmol) in tetrahydrofuran (60 ml) at 0°C, *n*-BuMgCl (2M solution in THF, 15.7 ml, 31.5 mmol) was added
20 over 10 minutes. After stirring for additional 20 minutes, the ice bath was removed and the solution was stirred for 2 hours. The reaction mixture was recooled to 0°C and triethylborane (1M solution in THF, 38 ml, 38 mmol) was added. After stirring for
25 1 hour, the reaction was heated to reflux for 72 hours. The reaction mixture was cooled to room temperature and treated with aqueous sodium acetate (5.5 g in 22 ml water). After stirring for 5 minutes, solid hydroxylamine-O-sulfonic acid (5.5 g)
30 was added and the mixture stirred for 24 hours. The reaction mixture was diluted with water and extracted with ether. The ethereal layer was dried

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over sodium sulfate, filtered and concentrated. The crude solid (13.3 g) was purified by chromatography (silica gel, hexane/isopropanol, 7/3) to give 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (298 mg, 12%): mp (DSC) 203°C. Anal. Calc'd. for $C_{16}H_{13}N_4SO_2F_3 \cdot 0.25 H_2O$: C, 49.68, H, 3.52, N, 14.48, S, 8.29. Found: C, 49.88, H, 3.39, N, 13.94, S, 8.47.

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Example 37



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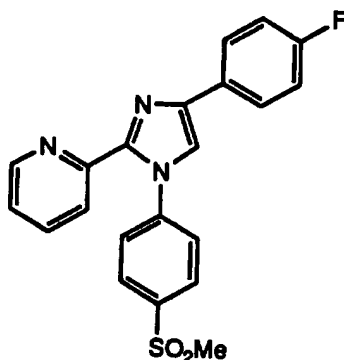
4-[2-(6-Methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide

To a clear solution of Example 32 (10 mmol) in tetrahydrofuran (60 ml) at 0°C, *n*-BuMgCl (2M solution in THF, 25 ml, 50 mmol) is added over 10 minutes. After stirring for an additional 20 minutes, the ice bath is removed and the solution is stirred for 2 hours. The reaction mixture is recooled to 0°C and triethylborane (1M solution in THF, 60 ml, 60 mmol) is added. After stirring for 1 hour, the reaction is heated to reflux for 72 hours. The reaction mixture is cooled to room temperature and treated with aqueous sodium acetate (5.5 g in 22 ml water). After stirring for 5 minutes, solid hydroxylamine-O-sulfonic acid (5.5 g) is added and the mixture stirred for 24 hours. The reaction mixture is diluted with water and extracted with

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ether. The ethereal layer is dried over sodium sulfate, filtered and concentrated. The crude solid is purified by chromatography on silica gel using mixtures of hexane and isopropanol to give the
5 desired product.

Example 38



10
2-[4-(4-Fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazol-2-yl]pyridine

15 Step 1: Preparation of N-[4-(methylsulfonyl)phenyl]-2-pyridinecarboximidamide

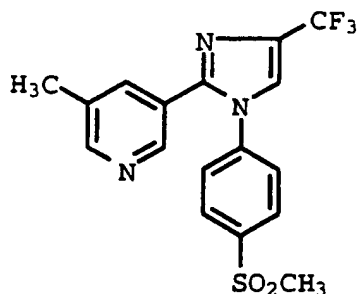
To a suspension of 5.00 g (24.0 mmol) of 4-methylsulfonylaniline hydrochloride in 150 ml of toluene stirring in an ice bath under nitrogen, was
20 added dropwise 18.0 ml (containing 36.0 mmol) of a 2M solution of trimethylaluminum in toluene. After stirring for 30 minutes, a solution of 3.75 g (36.0 mmol) of 2-cyanopyridine in 20 ml of toluene. The resulting solution was stirred overnight at room
25 temperature, and then at 85° for four hours. After cooling, the toluene was decanted and evaporated. The residue was taken up in 150 ml of methylene chloride and added back to the reaction flask. Methanol (150 ml) was cautiously added, and the mixture was filtered
30 through a bed of silica gel using 50-50

methanol/methylene chloride as eluent. Evaporation of the solvent gave the amidine (6.85 g) as a yellow solid, which was used in the next reaction without further purification.

5

Step 2: Preparation of 2-[4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazol-2-yl]pyridine

A mixture of the amidine of Step 1 (2.00 g, 7.27 mmol), 2-bromo-4'-fluoroacetophenone (3.16 g, 14.5 mmol) and sodium bicarbonate (1.22 g, 14.5 mmol) in isopropanol (70 ml) was stirred at reflux for two days. After cooling, the solvent was evaporated. The residue was partitioned between methylene chloride and aqueous sodium chloride, and the aqueous layer further extracted with methylene chloride. The combined organic extracts were dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue over silica gel using 40% ethyl acetate/toluene followed by a second chromatography over silica gel using 40% ethyl acetate/methylene chloride as eluant gave 2-[4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazol-2-yl]pyridine (190 mg) as a light tan solid: m.p. 88-91°C. Anal. Calc'd for $C_{21}H_{16}FN_3O_2S$ (M.W. 393.44): C, 64.11; H, 4.10, N, 10.68. Found: C, 63.80; H, 4.16, N, 10.23.

Example 39

5 **3-Methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine**

Step 1: Preparation of 5-methylnicotinic acid:

The 5-methylnicotinic acid was prepared by
10 the method of E. P. Kyba et al., *J. Org. Chem.*,
53, 3513-3521 (1988)]. To a solution of KMnO_4 in
water (1.1 L) was added lutidine (25.0 g, 0.233
mol) and the mixture was stirred mechanically at
45°C overnight. The reaction mixture was cooled
15 and filtered through Celite® to remove MnO_2 . The
filtrate was concentrated to about 150 mL and
acidified with a 2N HCl solution. White solid
precipitated and was removed by filtration and
washed with water (2 x 50 mL). The filtrate and
20 washings were evaporated to dryness. The residue
was boiled with ethanol (200 mL) and filtered
repeatedly. The combined filtrate was
concentrated to give of 5-methylnicotinic acid as
a white solid (14.8 g, 46%): mp 213-215°C.

25

Step 2: Preparation of 5-methylpyridinylcarboxamide

A solution of 5-methylnicotinic acid from
step 1 (14.5 g, 0.106 mol) in 125 mL of thionyl
chloride was heated to reflux for 5 hours. Excess
30 thionyl chloride was removed by distillation and
the residue was suspended in 75 mL of
dichloroethane. Ammonia was bubbled into the

mixture at -30°C for half hour and the mixture was stirred at room temperature overnight. Solvent was evaporated and the residue was treated with methanol and filtered. The filtrate was

5 concentrated and the residue was extracted with boiling hot ethyl acetate (3 x 150 mL) to separate product from ammonium chloride. The extracts were filtered and concentrated to afford 10.6 g of 5-methylpyridinylcarboxamide as a brown solid (73%):

10 mp 160-163°C.

Step 3: Preparation of 3-cyano-5-methylpyridine

To a suspension of 5-methylpyridinylcarboxamide from step 2 (10.5 g, 0.077 mol) in triethylamine (23.3 g, 0.23 mol) and

15 400 mL of methylene chloride was added trifluoroacetic anhydride (21.0 g, 0.100 mol) rapidly at 0°C. The reaction was completed after a few minutes. Water was added and the aqueous

20 layer was extracted with methylene chloride. The combined organic layers were washed with water, brine and dried over magnesium sulfate. After filtration, the filtrate was concentrated to give 9.18 g of 3-cyano-5-methylpyridine crude, which

25 was used in the next step without purification.

Step 4: Preparation of 3-methyl-5-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine

To a suspension of 4-(methylsulfonyl)aniline hydrochloride (10.5 g, 0.051 mol) in toluene (500 mL) was added trimethylaluminum (2M solution in toluene, 75.0 mL, 0.150 mol) over 15 minutes at

30 0°C. The reaction mixture was warmed up to room temperature and stirred for 2 hours. A solution of 3-cyano-5-methylpyridine from step 3 in 90 mL of toluene was added over 10 minutes and the

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mixture was stirred at 85-90°C for 16 hours. The reaction mixture was cooled to room temperature and filtered through a slurry of silica gel. After filtration, the residue was washed with
5 methanol (800 mL). The combined filtrate was concentrated under reduced pressure and the residue was treated with a mixture of ether and hexane (2/1, 1000 mL). The brownish solid was filtered and washed with more ether and hexane to
10 give 11.8 g of N-[4-(methylsulfonyl)phenyl]-5-methylnicotinamide (80%). To a mixture of the above crude amidine (11.3 g, 0.039 mol) and sodium bicarbonate (9.83 g, 0.12 mol) in isopropanol (400 mL) was added 3-bromo-1,1,1-trifluoroacetone (11.2
15 g, 0.059 mol) quickly at room temperature. After heating the reaction mixture at 75-80°C for 16 hours, the solvent was removed and the residue was partitioned between water and methylene chloride. The organic layers were washed with brine, dried
20 over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (ethyl acetate/acetone, 98:2) to give pure 3-methyl-5-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-
25 4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine as a yellow solid (3.85 g, 25%): mp (DSC) 237-239°C; Anal. Calc'd. for C₁₇H₁₆F₃N₃O₃S: C, 51.12, H, 4.04, N, 10.52, S, 8.03. Found: C, 51.02, H, 3.94, N, 10.19, S, 8.11.

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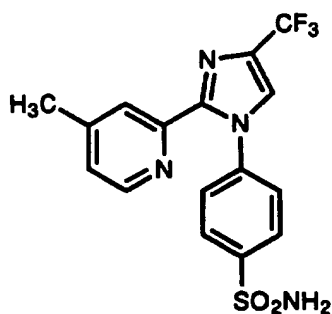
Step 5: Preparation of 3-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine

A mixture of 3-methyl-5-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine from step 4 (3.8
35 g, 9.5 mmol) and p-toluenesulfonic acid

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monohydrate (0.91 g, 4.8 mmol) in 150 mL of toluene was heated to reflux for 24 hours. The reaction mixture was cooled and the solvent was removed under reduced pressure. The residue was partitioned between water and methylene chloride. The organic layer was washed with water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and filtered. The filtrate was evaporated in vacuo and the crude product was purified by flash chromatography on silica gel (ethyl acetate/acetone, 98:2) to give 3-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine as a yellow solid (1.7 g, 47%): mp (DSC) 196-198°C; Anal. Calc'd. for $C_{17}H_{14}F_3N_3O_2S$: C, 53.54, H, 3.70, N, 11.02, S, 8.41. Found: C, 53.50, H, 3.65, N, 10.82, S, 8.55.

Example 40



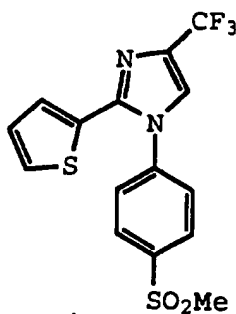
4-[2-(4-Methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide

To a stirred solution of the product of Example 34 (294.5 mg, 0.77 mmol) in 11 ml of freshly distilled THF at 0 °C was added 1.54 ml of butyl magnesium chloride (2.0 M solution in THF) over a period of 6 minutes. After stirring at 25 °C for 2.5 hours, the reaction was

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cooled to 0 °C and 3.85 ml of triethylborane (1.0 M solution in THF) was added over 30 minutes. The reaction mixture was stirred at 25°C for 1.5 hours and heated to reflux. After 72 hours, the reaction mixture was diluted with 50 ml of ethyl acetate and washed with aqueous sodium bicarbonate (2 x 50 ml). The organic extracts were dried (MgSO₄), filtered and the solvent removed under reduced pressure to provide 359 of an orange solid, which was purified by chromatography (SiO₂; 40% toluene/ethyl acetate) to provide 68.1 mg of a light yellow solid. Preparative thin layer chromatography (SiO₂; 50% ethyl acetate/toluene) of 22 mg of this material yielded 14 mg of 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide: mp (DSC) 283 °C. Anal. Calc'd. for C₁₆H₁₃F₃N₄O₂S: C, 50.26; H, 3.43; N, 14.65; S, 8.50. Found: C, 50.41; H, 3.37; N, 14.18; S, 8.51.

Example 41



2-[1-[4-(Methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]thiophene

Step 1: Preparation of N-[4-(methylsulfonyl)phenyl]-2-thiophenecarboximidamide

To a suspension of 4-(methylsulfonyl)aniline (10.4 g, 61.1 mmol) in toluene (400 ml) at 0°C, trimethylaluminum (2M solution in toluene, 46.8 ml, 91.6 mmol) was added over 15 minutes. The reaction

mixture was warmed to room temperature and stirred for 2 hours. A solution of 2-thiophenecarbonitrile (10.0 g, 91.6 mmol) in toluene (200 ml) was added over 10 minutes and the mixture was heated to 80-85°C. After 16 hours, the reaction mixture was cooled to room temperature and poured over a slurry of silica gel in chloroform. After filtration, the residue was washed with a mixture of methylene chloride/methanol and later with methanol. The combined filtrates were concentrated and the resulting yellow solid was stirred with ethyl acetate and filtered. The pale yellow solid (9.8 g, 57%) was used in the next reaction without further purification: m.p. (DSC) 182°C. Anal. Calc'd. for $C_{12}H_{12}N_2S_2O_2$: C, 51.41, H, 4.31, N, 9.99, S, 22.87. Found: C, 51.02, H, 4.37, N, 9.80, S, 22.93.

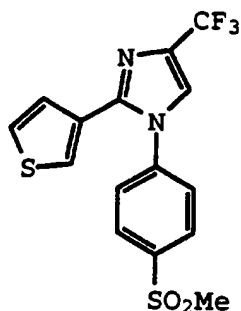
Step 2: Preparation of 2-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]thiophene

To a mixture of the amidine of step 1 (2.0 g, 7.1 mmol) and sodium bicarbonate (1.2 g, 14.3 mmol) in isopropanol (200 ml), 3-bromo-1,1,1-trifluoroacetone (1.1 ml, 10.7 mmol) was added. After heating at 80-85°C for 16 hours, the reaction mixture was cooled and filtered. The residue was washed with methylene chloride and the combined organic fractions were dried over sodium sulfate, filtered and concentrated. The crude mixture (25.7 g) was purified by chromatography (silica gel, ethyl acetate/hexane 55/45) to give the 4,5-dihydro-imidazole (1.1 g, 38%) as a white solid: mp (DSC) 214°C. Anal. Calc'd. for $C_{15}H_{13}N_2S_2O_3F_3$: C, 46.15, H, 3.36, N, 7.18, S, 16.43. Found: C, 46.09, H, 3.26, N, 7.07, S, 16.71.

Step 3: Preparation of 2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]thiophene

A mixture of the 4,5-dihydro-imidazole of step 2 (0.60 g, 1.54 mmol) and p-toluenesulfonic acid monohydrate (0.12 g, 0.63 mmol) in toluene (100 ml) was heated to reflux for 4.5 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude mixture (1.2 g) was purified by chromatography on silica gel using ethyl acetate/hexane 50/50 to give pure 2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]thiophene (0.47 g, 82%) as a white solid: mp (DSC) 182°C. Anal. Calc'd. for C₁₅H₁₁N₂S₂O₂F₃ C, 48.38, H, 2.98, N, 7.52, S, 17.22. Found: C, 48.36, H, 3.02, N, 7.42, S, 17.47.

Example 42



3-[1-[4-(Methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]thiophene

20 Step 1: Preparation of N-[4-(methylsulfonyl)phenyl]-2-thiophenecarboximidamide

To a suspension of 4-(methylsulfonyl)aniline (3.3 g, 19.5 mmol) in toluene (200 ml) at 0°C, trimethylaluminum (2M solution in toluene, 14.7 ml, 29.3 mmol) was added over 15 minutes. The reaction mixture was warmed to room temperature and stirred for 2 hours. A solution of 3-thiophenecarbonitrile (3.2 g, 29.3 mmol) in toluene (50 ml) was added over 10 minutes and the mixture was heated to 80-85°C. After 16 hours, the reaction mixture was cooled to room temperature and poured over a slurry of silica gel in chloroform. After

filtration, the residue was washed with a mixture of methylene chloride/methanol and later with methanol. The combined filtrates were concentrated and the resulting yellow solid was stirred with ethyl acetate and filtered. The pale yellow solid (2.7 g, 49%) was used in the next reaction without further purification: mp (DSC) 213 °C, Anal. Calc'd. for $C_{12}H_{12}N_2S_2O_2$: C, 51.41, H, 4.31, N, 9.99, S, 22.87. Found: C, 51.28, H, 4.06, N, 9.86, S, 23.14.

Step 2: Preparation of 3-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]thiophene

To a mixture of the amidine of step 1 (3.5 g, 12.5 mmol) and sodium bicarbonate (2.1 g, 25.0 mmol) in isopropanol (200 ml), 3-bromo-1,1,1-trifluoroacetone (1.96 ml, 18.7 mmol) was added. After heating at 80-85°C for 16 hours, the reaction mixture was cooled and filtered. The residue was washed with methylene chloride and the combined organic fractions were dried over sodium sulfate, filtered and concentrated. The crude material was purified by chromatography (silica gel, ethyl acetate/toluene (6/4)) to give 3-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]thiophene (1.7 g, 35%) as a white solid: mp (DSC) 226°C. Anal. Calc'd. for $C_{15}H_{13}N_2S_2O_3F_3$: C, 46.15, H, 3.36, N, 7.18, S, 16.43. Found: C, 46.56, H, 3.39, N, 7.01, S, 16.88.

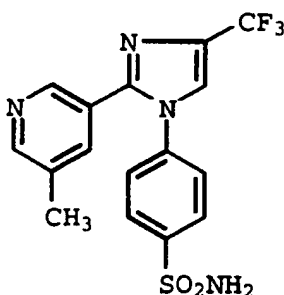
Step 3: Preparation of 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]thiophene

A mixture of the 4,5-dihydro-imidazole of step 2 (1.5 g, 3.8 mmol) and p-toluenesulfonic acid monohydrate (0.30 g, 1.5 mmol) in toluene (250 ml) was heated to reflux for 40 hours. An additional p-

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toluenesulfonic acid monohydrate (0.15 g, 0.78 mmol) was added. The reaction mixture was heated to reflux for 18 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude mixture (3.5 g) was purified by chromatography on silica gel using ethyl acetate/toluene (55/45) to give pure 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]thiophene (0.90 g, 64%) as a white solid: mp 194-197°C. Anal. Calc'd. for $C_{15}H_{11}N_2S_2O_2F_3$: C, 48.38, H, 2.98, N, 7.52, S, 17.22. Found: C, 48.74, H, 2.98, N, 7.56, S, 17.45 .

Example 43



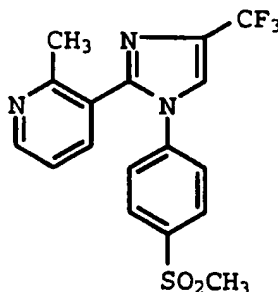
4-[2-(5-Methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide

To a solution of 3-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (Example 39) (1.9 mmol) in 25 mL of dry THF was added n-BuMgCl (3.8 mL of 2.0 M THF solution, 7.5 mmol) slowly at 0 °C. After stirring for additional 15 minutes, the solution was stirred at room temperature for 2 hours. The reaction mixture was re-cooled to 0°C and triethylborane (9.5 mL of 1.0 M THF solution, 9.5 mmol) was added. After stirring at for 2 hours, the mixture was heated to reflux for 72 hours. The reaction mixture was cooled to room temperature and treated with a solution of sodium acetate (2.3 g) in 10 mL of water. After stirring for 5 minutes, hydroxylamine-O-sulfonic acid (2.3 g) was

added and the mixture was stirred for 20 hours. The reaction mixture was extracted with ether (2 x 100 mL). The ethereal layer was dried over MgSO_4 , filtered and concentrated in vacuo. The crude product was purified by chromatography on silica gel (isopropanol/toluene, 5:95) to give 0.07 g of 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide as a colorless solid (8%): mp 242-243°C. Anal. Calc'd. For $\text{C}_{16}\text{H}_{13}\text{F}_3\text{N}_4\text{O}_2\text{S}$: C, 50.26, H, 3.43, N, 14.65, S, 8.39.

Found: C, 50.02, H, 3.63, N, 14.26, S, 8.41.

Example 44



15

2-Methyl-3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine

Step 1: Preparation of 2-methylnicotinamide:

To a stirred mixture of 2-methylnicotinic acid (15.0 g, 0.111 mol) and 1,1'-carbonyldiimidazole (36.0 g, 0.222 mol) was added 300 mL of methylene chloride dropwise. The reaction mixture was stirred at room temperature overnight. Ammonia gas was distilled into the reaction mixture for 30 minutes using a dry ice condenser and the mixture was stirred at room temperature for an additional hour. Solvent was removed under vacuum and the residue was dissolved with 500 mL of acetonitrile. The solution was concentrated to half volume at low temperature and the product precipitated out as white solid. The crude mixture was recrystallized from ethanol/ether to give 11.5 g of 2-

methylnicotinamide as a colorless crystal (76%): mp 160-163°C. Anal. Calc'd. For $C_7H_8N_2O$: C, 61.75, H, 5.92, N, 20.57. Found: C, 61.44, H, 6.14, N, 20.66.

5 Step 2: Preparation of 3-cyano-2-methylpyridine:

To a suspension of 2-methylnicotinamide from step 1 (11.1 g, 0.081 mol) in triethylamine (24.8 g, 0.243 mol) and 400 mL of methylene chloride was added trifluoroacetic anhydride (21.0 g, 0.100 mol) rapidly at 0°C. The reaction
10 was complete after a few minutes at this temperature. Water was added and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with water, brine and dried over magnesium sulfate. After filtration, the filtrate was concentrated and the
15 residue was purified by chromatography on silica gel (ethyl acetate/hexane, 1:1) to give 7.2 g of 3-cyano-2-methylpyridine as a pale yellow solid (75%): mp(DSC) 56-58°C.

20 Step 3: Preparation of 2-methyl-3-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine:

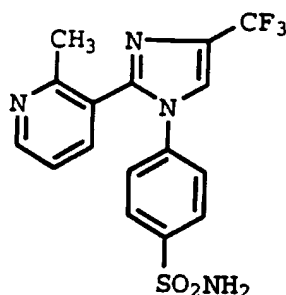
To a suspension of 4-(methylsulfonyl)aniline hydrochloride (6.85 g, 0.040 mol) in dichloroethane (400
25 mL) was added triethylaluminum (1.9M solution in toluene, 32.0 mL, 60 mmol) over 15 minutes at 0°C. The reaction mixture was warmed to room temperature and stirred for 2 hours. A solution of 3-cyano-2-methylpyridine, from step 2, in 70 mL of dichloroethane was added over 10 minutes and
30 the mixture was stirred at 75°C for 16 hours. The reaction mixture was cooled to room temperature and stirred with 50 g of silica gel. The mixture was stirred for 15 minutes and filtered. The filtrate and washings were concentrated under reduced pressure and the residue was washed with
35 ether to give 7.3 g of crude 2-methyl-N-[4-(methylsulfonyl)phenyl]-3-pyridinecarboximidate (50%). To a mixture of the above crude amidine (7.0 g, 4 mol)

and sodium bicarbonate (4.0 g, 0.048 mol) in isopropanol (350 mL) was added 3-bromo-1,1,1-trifluoroacetone (6.9 g, 0.036 mol) rapidly at room temperature. After heating the reaction mixture at 75-80°C for 16 hours, the solvent was removed and the residue was partitioned between water and methylene chloride. The organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (ethyl acetate/acetone, 98:2) to give 4.02 g of pure 2-methyl-3-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine as a yellow solid (25%): mp (DSC) 237-239°C. Anal. Calc'd. for $C_{17}H_{16}F_3N_3O_3S$: C, 51.12, H, 4.04, N, 10.52, S, 8.03. Found: C, 50.92, H, 4.12, N, 10.04, S, 7.83.

Step 4: Preparation of 2-methyl-3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine:

A mixture of 2-methyl-3-[4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazol-2-yl]pyridine from step 3 (3.97 g, 0.01 mol) and p-toluenesulfonic acid monohydrate (0.60 g, 0.0032 mol) in 250 mL of toluene was heated to reflux for 24 hours. The reaction mixture was cooled and the solvent was removed under reduced pressure. The residue was partitioned between water and methylene chloride. The organic layer was washed with water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and filtered. The filtrate was evaporated in vacuo and the crude product was purified by recrystallization from ethyl acetate/hexane to give 2.8 g of 2-methyl-3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (73%): mp 160-161°C. Anal. Calc'd. for $C_{17}H_{14}F_3N_3O_2S$: C, 53.54, H, 3.70, N, 11.02, S, 8.41. Found: C, 53.58, H, 3.88, N, 11.02, S, 8.51.

Example 45



5 **4-[2-(2-Methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide**

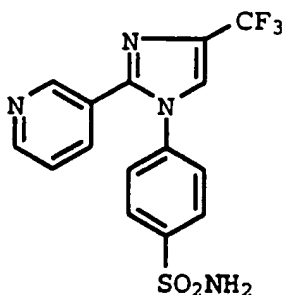
10 Step 1: Preparation of 2-methyl-3-[1-[4-[2-(trimethylsilyl)ethyl]sulfonyl]phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine

To a solution of diisopropylamine (0.7 mL, 0.005 mol) in 9 mL of dry THF was added butyllithium (BuLi) (2.83 mL of 1.62M solution in hexane, 4.6 mmol) at 0°C. The solution was stirred at this temperature for 5 minutes and cooled to -78°C with a dry ice/isopropanol bath. A solution of 2-methyl-3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (Example 44) (1.46 g, 3.8 mmol) in 12 mL of dry THF was added over 10 minutes and the reaction mixture was stirred at -78°C for 1 hour. (Iodomethyl)trimethylsilane (1.23 g, 57 mmol) was added dropwise and the reaction mixture was warmed to room temperature and was stirred overnight. The reaction was quenched with 50 mL of 1 N HCl and the aqueous phase was extracted with ethyl acetate (3 x 60 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated. The crude mixture was purified by chromatography on silica gel (ethyl acetate/hexane, 65:35) to give 1.30 g of 2-methyl-3-[1-[4-[2-(trimethylsilyl)ethyl]sulfonyl]phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine as a white solid (74%): mp(DSC)

155-157°C. Anal. Calc'd. for $C_{21}H_{24}F_3N_3O_2SSi$: C, 53.94; H, 5.17; N, 8.99; S, 6.86. Found: C, 53.77; H, 4.94; N, 8.75; S, 6.98.

5 Step 2: Preparation of 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide:

To a solution of 2-methyl-3-[1-[4-[[2-(trimethylsilyl)ethyl]sulfonyl]phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine from Step 1 (0.234 g, 0.5 mmol)
10 in 1.5 mL of dry THF was added $n\text{-Bu}_4\text{NF}$ (1.5 mL of 1.0M THF solution, 1.5 mmol). The mixture was heated to reflux for 1 hour and cooled to room temperature. A solution of sodium acetate (0.19 g, 2.3 mmol) in 3 mL of water and hydroxylamine-O-sulfonic acid (0.28 g, 2.5 mmol) were added
15 sequentially and the mixture was stirred for 1 hour. Water (7 mL) and ethyl acetate (7 mL) were added. The organic phase was separated and washed with sat. NaHCO_3 solution, water, and brine, dried over MgSO_4 and filtered. The filtrate was concentrated and the residue was purified by
20 chromatography on silica gel (ethyl acetate/acetone, 95:5) to give 0.16 g of 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide as a colorless solid (84%): mp 235-237°C. Anal. Calc'd. for $C_{16}H_{13}F_3N_4O_2S$: C, 50.26; H, 3.43; N, 14.65; S, 8.39.
25 Found: C, 50.06; H, 3.29; N, 14.44; S, 8.52.

Example 46

5 **4-[2-(Pyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide**

3-[1-[4-[[2-(Trimethylsilyl)ethyl]sulfonyl]phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine was
10 prepared with the product of Example 28 with a method similar to that described in Example 45, Step 1. To a solution of 3-[1-[4-[[2-(trimethylsilyl)ethyl]sulfonyl]phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (0.200 g,
15 0.46 mmol) in 1.0 mL of dry THF was added n-Bu₄NF (1.38 mL of 1.0 M THF solution, 1.38 mmol). The mixture was heated to reflux for 1 hour and cooled to room temperature. A solution of sodium acetate (0.17 g, 2.1 mmol) in 3 mL of water and hydroxylamine-O-sulfonic
20 acid (0.26 g, 2.3 mmol) were added sequentially and the mixture was stirred for 1 hour. Water (7 mL) and ethyl acetate (7 mL) were added. The organic phase was separated and washed with saturated NaHCO₃ solution, water, brine, dried over MgSO₄ and filtered. The
25 filtrate was concentrated and the residue was purified by chromatography on silica gel (ethyl acetate/acetone, 95:5) to give 0.147 g of 4-[2-(pyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide as a colorless solid (87%): mp(DSC) 213-215 °C. Anal.
30 Calc'd. for C₁₅H₁₁F₃N₄O₂S: C, 48.91; H, 3.01; N, 15.21; S, 8.71. Found: C, 48.58; H, 2.99; N, 14.87; S, 8.85.

The following imidazole derivatives could be prepared by the procedure described in Example 26 or 45:

- 5 Example 47: 4-[2-(4-chlorophenyl)-4-methyl-1H-imidazol-1-yl]benzenesulfonamide;
- Example 48: 4-[2-(4-chlorophenyl)-4-phenyl-1H-imidazol-1-yl]benzenesulfonamide;
- Example 49: 4-[2-(4-chlorophenyl)-4-(4-
- 10 fluorophenyl)-1H-imidazol-1-yl]benzenesulfonamide;
- Example 50: 4-[2-(4-chlorophenyl)-4-(4-bromophenyl)-1H-imidazol-1-yl]benzenesulfonamide;
- Example 51: 4-[2-(4-chlorophenyl)-4-(2-naphthyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 15 Example 52: 4-[2-(4-chlorophenyl)-4-[4-(trifluoromethoxy)phenyl]-1H-imidazol-1-yl]benzenesulfonamide;
- Example 53: 4-[2,4-bis(4-chlorophenyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 20 Example 54: 4-[2-(4-chlorophenyl)-4-(3-chlorophenyl)-1H-imidazol-1-yl]benzenesulfonamide;
- Example 55: 4-[2-(4-chlorophenyl)-4-[4-(methoxy)phenyl]-1H-imidazol-1-yl]benzenesulfonamide;
- Example 56: 4-[2-(4-chlorophenyl)-4-(3-
- 25 fluorophenyl)-1H-imidazol-1-yl]benzenesulfonamide;
- Example 57: 4-[2-(4-chlorophenyl)-4-[(4-chlorophenoxy)methyl]-1H-imidazol-1-yl]benzenesulfonamide;
- Example 58: 4-[2-(3,4-methylenedioxyphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 30 Example 59: 4-[2-(3-fluoro-4-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- Example 60: 4-[2-(4-chlorophenyl)-4-[(phenylthio)methyl]-1H-imidazol-1-
- 35 yl]benzenesulfonamide;

Example 61: 4-[2-(4-chlorophenyl)-4-[(N-methyl-N-phenylamine)methyl]-1H-imidazol-1-yl]benzenesulfonamide;

5 Example 62: 4-[2-(4-chlorophenyl)-4-[(2-quinolylmethoxy)methyl]-1H-imidazol-1-yl]benzenesulfonamide;

Example 63: 4-[2-(4-chlorophenyl)-4-methoxymethyl-1H-imidazol-1-yl]benzenesulfonamide;

10 Example 64: 4-[2-(4-fluorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

Example 65: 4-[2-phenyl-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide; and

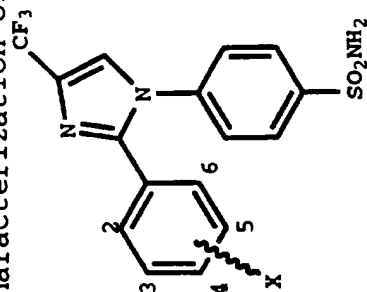
15 Example 66: 4-[2-(4-trifluoromethylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide.

The following imidazole derivative was prepared by the procedure described in Example 28:

20 Example 67: 1-methyl-3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]-1H-indole.

25 The following imidazole derivatives in Tables I-IV were obtained according to procedures of Schemes I-XIV. Many of these were synthesized by using the experimental conditions given in Examples 1-5. The sulfonamide derivatives were synthesized from the corresponding sulfones using experimental procedure given for Examples 26-27 and 45.

Table I: Characterization of Compounds

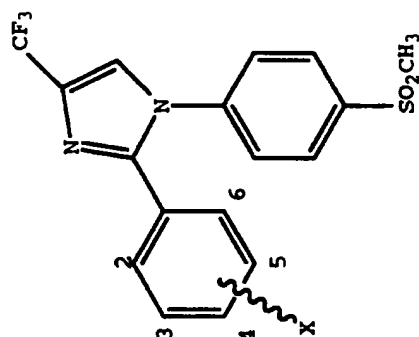


| Example | X | mp DSC (°C) | Elemental Analysis | | | | | | | |
|---------|-----------------------------|----------------|--------------------|------|-------|------|-------|------|-------|------|
| | | | Calc'd | | | | Found | | | |
| | | | C | H | N | S | C | H | N | S |
| 68 | 4-CH ₃ | 263 | 53.54 | 3.70 | 11.02 | 8.41 | 53.91 | 3.62 | 10.71 | 8.57 |
| 69 | 3-CH ₃ | 222.9 | 53.54 | 3.70 | 11.02 | 8.41 | 53.81 | 3.56 | 10.89 | 8.54 |
| 70 | 3-Cl | 204.1 | 47.82 | 2.76 | 10.46 | 7.98 | 48.09 | 2.50 | 10.09 | 8.16 |
| 71 | 3,5-diF, 4-OCH ₃ | 245.1 | 57.27 | 3.85 | 10.02 | 7.64 | 56.94 | 3.77 | 9.78 | 7.50 |
| 72 | H | 234-235 | 52.31 | 3.29 | 11.44 | 8.71 | 52.40 | 3.27 | 11.06 | 8.44 |
| 73 | 3,4-diF | 215.9 | 47.65 | 2.50 | 10.42 | 7.95 | 47.68 | 2.44 | 10.25 | 8.07 |
| 74 | 3-Cl, 4-OCH ₃ | 212.0 | 47.29 | 3.03 | 9.73 | 7.43 | 47.41 | 2.76 | 9.49 | 7.48 |
| 75 | 3-F | 204-205 | 49.74 | 3.13 | 10.88 | 8.30 | 49.99 | 2.95 | 10.49 | 8.45 |
| 76 | 4-Cl, 5-OCH ₃ | 208-209 | 47.29 | 3.03 | 9.73 | 7.43 | 47.21 | 2.95 | 9.62 | 7.73 |
| 77 | 3-F, 5-OCH ₃ | 208.8 | 49.16 | 3.15 | 10.12 | 7.72 | 49.31 | 2.95 | 9.84 | 7.88 |

Table I: Characterization of Compounds (cont.)

| Example | X | mp DSC (°C) | Elemental Analysis | | | | | | | | |
|---------|--------------------------|----------------|--------------------|------|-------|-------|-------|------|-------|-------|--|
| | | | Calc'd | | | | | | Found | | |
| | | | C | H | N | S | C | H | N | S | |
| 78 | 3-Br, 4-OCH ₃ | 208-210 | 41.69 | 2.98 | 8.58 | 6.55 | 41.52 | 2.9 | 7.81 | 6.14 | |
| 79 | 2-F | 169-171 | 49.87 | 2.88 | 10.9 | 8.32 | 49.5 | 2.83 | 10.34 | 8.61 | |
| 80 | 3-Br | 203-205 | 43.07 | 2.48 | 9.42 | 7.19 | 42.71 | 2.44 | 8.94 | 6.68 | |
| 81 | 3-Cl, 4-SCH ₃ | 205-207 | 45.59 | 2.93 | 9.38 | 14.32 | 46.00 | 3.11 | 8.96 | 14.29 | |
| 82 | 3-Cl, 5-CH ₃ | 219-221 | 49.1 | 3.15 | 10.11 | 7.71 | 49.44 | 3.11 | 9.7 | 7.89 | |
| 83 | 3-F, 5-CH ₃ | 230-231 | 51.13 | 3.28 | 10.52 | 8.03 | 51.49 | 3.51 | 10.00 | 8.15 | |
| 84 | 3-CF ₃ | 208.8 | 46.90 | 2.55 | 9.65 | 7.37 | 47.30 | 2.54 | 9.47 | 7.49 | |

Table II: Characterization of Compounds



| Example | X | mp DSC (°C) | Elemental Analysis | | | | | | | | |
|---------|-----------------------------|----------------|--------------------|------|------|-------|-------|------|------|------|---|
| | | | Calc'd | | | Found | | | C | H | S |
| | | | C | H | N | S | C | H | | | |
| 85 | 3,4-diF | 159.5 | 50.75 | 2.76 | 6.96 | 8.80 | 50.66 | 2.82 | 6.87 | 8.30 | |
| 86 | 3-CH ₃ | 169.8 | 56.84 | 3.97 | 7.36 | 8.43 | 56.88 | 3.76 | 7.26 | 8.81 | |
| 87 | 3-Cl | 175.4 | 50.94 | 3.02 | 6.99 | 8.00 | 51.06 | 3.06 | 6.93 | 8.13 | |
| 88 | 3-F | 189.3 | 53.13 | 3.15 | 7.29 | 8.34 | 53.50 | 3.16 | 7.22 | 8.46 | |
| 89 | 4-F, 3-CH ₃ | 166.9 | 54.27 | 3.54 | 7.03 | 8.05 | 54.47 | 3.40 | 6.88 | 8.31 | |
| 90 | 3-CF ₃ | 168.2 | 49.77 | 2.78 | 6.45 | 7.38 | 49.91 | 2.60 | 6.34 | 7.68 | |
| 91 | 3,5-diF, 4-OCH ₃ | 174.7 | 50.00 | 3.03 | 6.48 | 7.42 | 50.00 | 3.03 | 6.33 | 7.44 | |

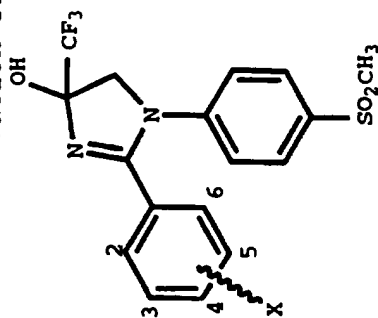
Table II: Characterization of Compounds (cont.)

| Example | X | mp DSC(°C) | Elemental Analysis | | | | | | | |
|---------|--|---------------|--------------------|------|-------|-------|-------|------|-------|-------|
| | | | Calc'd | | | | Found | | | |
| | | | C | H | N | S | C | H | N | S |
| 92 | 3-CH ₂ OCH ₃ | 101.9 | 55.60 | 4.18 | 6.83 | 7.81 | 55.50 | 4.14 | 6.72 | 8.06 |
| 93 | 3-Cl, 4-OCH ₃ | 193.3 | 50.18 | 3.28 | 6.50 | 7.44 | 49.78 | 3.32 | 6.39 | 7.42 |
| 94 | 3,4-diCH ₃ | 187-188 | 57.86 | 4.34 | 7.10 | 8.13 | 57.59 | 4.23 | 7.20 | 8.05 |
| 95 | 4-OCH ₃ | 167.5 | 54.54 | 3.81 | 7.07 | 8.09 | 54.32 | 3.88 | 6.90 | 8.24 |
| 96 | 3-OCH ₃ | 143.2 | 54.54 | 3.81 | 7.07 | 8.09 | 54.27 | 3.82 | 6.91 | 8.31 |
| 97 | 4-Cl, 5-OCH ₃ | 215.3 | 50.18 | 3.28 | 6.50 | 7.44 | 50.20 | 3.20 | 6.23 | 7.76 |
| 98 | 3-F, 5-OCH ₃ | 178-179 | 52.17 | 3.41 | 6.76 | 7.74 | 52.07 | 3.29 | 6.66 | 7.87 |
| 99 | 4-SCH ₃ | 193-195 | 52.42 | 3.67 | 6.79 | 15.55 | 52.19 | 3.63 | 6.61 | 15.55 |
| 100 | 4-SO ₂ CH ₃ | 215-216 | 48.64 | 3.4 | 6.3 | 14.43 | 48.87 | 3.47 | 6.24 | 14.36 |
| 101 | 3,5-CH ₃ , 4-OCH ₃ | 167-169 | 56.6 | 4.51 | 6.6 | 7.55 | 56.04 | 4.61 | 6.44 | 7.72 |
| 102 | 2,5-CH ₃ , 4-OCH ₃ | 193-194 | 56.6 | 4.51 | 6.6 | 7.55 | 56.63 | 4.65 | 6.47 | 7.99 |
| 103 | 2-F | 191-192 | 53.13 | 3.15 | 7.29 | 8.34 | 53.55 | 3.55 | 6.89 | 8.55 |
| 104 | 2-Cl | 201-203 | 50.94 | 3.02 | 6.99 | 8.00 | 50.86 | 3.06 | 6.88 | 7.83 |
| 105 | 4-N(CH ₃) ₂ | 219-221 | 55.74 | 4.43 | 10.26 | 7.83 | 55.19 | 4.00 | 10.06 | 7.81 |
| 106 | 3-F, 4-N(CH ₃) ₂ | 163-164 | 53.59 | 4.01 | 9.83 | 7.5 | 53.48 | 3.79 | 9.73 | 7.67 |
| 107 | 3-Br | 163-165 | 45.86 | 3.73 | 6.29 | 7.2 | 45.84 | 2.59 | 6.16 | 7.37 |
| 108 | 3-NO ₂ | 207-209 | 49.64 | 2.94 | 10.21 | 7.79 | 49.48 | 3.01 | 10.07 | 7.81 |

Table II: Characterization of Compounds (cont.)

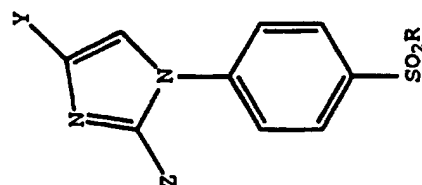
| Example | X | mp DSC (°C) | Elemental Analysis | | | | | | | | |
|---------|--|----------------|--------------------|------|-------|-------|-------|------|-------|-------|--|
| | | | Calc'd | | | | | | Found | | |
| | | | C | H | N | S | C | H | N | S | |
| 109 | 4-NH(CH ₃) | 200-202 | 54.68 | 4.08 | 10.63 | 8.11 | 54.74 | 3.98 | 10.42 | 7.96 | |
| 110 | 3-NH ₂ | 218-200 | 53.54 | 3.7 | 11.02 | 8.41 | 52.92 | 3.58 | 10.67 | 8.6 | |
| 111 | 3-NH(CH ₃) | 90-92 | 54.68 | 4.08 | 10.63 | 8.11 | 54.56 | 4.12 | 10.28 | 8.09 | |
| 112 | 3-F, 4-NH(CH ₃) | 205-206 | 52.3 | 3.66 | 10.16 | 7.76 | 51.74 | 3.51 | 9.96 | 7.99 | |
| 113 | 3-SCH ₃ | 135-137 | 52.42 | 3.67 | 6.79 | 15.55 | 52.29 | 3.57 | 6.74 | 15.22 | |
| 114 | 3-Cl, 5-CH ₃ | 171-173 | 52.12 | 3.4 | 6.75 | 7.73 | 51.95 | 3.22 | 6.69 | 7.9 | |
| 115 | 3,5-Cl, 4-OCH ₃ | 198-202 | 46.47 | 2.82 | 6.02 | 15.24 | 46.49 | 2.77 | 5.8 | 14.73 | |
| 116 | 3-F, 4-CH ₃ | 173-176 | 54.27 | 3.54 | 7.03 | 8.05 | 54.65 | 3.64 | 6.74 | 8.14 | |
| 117 | 3-F, 5-CH ₃ | 178-181 | 54.27 | 3.54 | 7.03 | 8.05 | 53.85 | 3.29 | 6.81 | 8.3 | |
| 118 | 4-Cl, 3-CH ₃ | 182-184 | 52.12 | 3.4 | 6.25 | 7.73 | 52.36 | 3.49 | 6.78 | 7.95 | |
| 119 | 3-Cl, 4-N(CH ₃) ₂ | 178-179 | 51.41 | 3.86 | 9.47 | 7.22 | 51.44 | 3.65 | 9.34 | 7.28 | |
| 120 | 3-Cl, 4-SCH ₃ | 181-184 | 48.38 | 3.16 | 6.27 | 14.35 | 47.9 | 3.05 | 5.97 | 13.84 | |
| 121 | 2-CH ₃ | 132-134 | 56.84 | 3.97 | 7.36 | 8.43 | 56.75 | 3.82 | 7.28 | 8.59 | |
| 122 | 3-N(CH ₃) ₂ | 170-171 | 55.74 | 4.43 | 10.26 | 7.83 | 55.66 | 4.66 | 9.95 | 7.7 | |

Table III: Characterization of Compounds



| Example | X | mp DSC (°C) | Elemental Analysis | | | | | | | |
|---------|---|----------------|--------------------|------|------|------|-------|------|------|-------|
| | | | Calc'd | | | | Found | | | |
| | | | C | H | N | S | C | H | N | S |
| 123 | 3-Cl, 4-OCH ₃ | 222.1 | 48.17 | 3.59 | 6.24 | 7.14 | 48.11 | 3.83 | 5.80 | 7.21 |
| 124 | 3-CH ₃ , 4-OCH ₃ | 173.7 | 54.85 | 4.70 | 6.73 | 7.71 | 54.65 | 4.45 | 6.58 | 8.30 |
| 125 | 4-OCH ₃ | 168.5 | 52.17 | 4.13 | 6.76 | 7.74 | 52.32 | 4.20 | 6.52 | 7.84 |
| 126 | 3-OCH ₃ | 176.4 | 52.17 | 4.13 | 6.76 | 7.74 | 51.80 | 4.12 | 6.55 | 8.02 |
| 127 | 4-Cl, 5-OCH ₃ | 137-138 | 46.85 | 3.80 | 6.07 | 6.95 | 46.45 | 3.72 | 5.84 | 7.25 |
| 128 | 3-F, 5-OCH ₃ | 185-186 | 50.00 | 3.73 | 6.48 | 7.42 | 50.12 | 3.78 | 6.36 | 7.70 |
| 129 | 4-SCH ₃ | 187-190 | 50.22 | 3.98 | 6.51 | 14.9 | 49.99 | 3.88 | 6.32 | 14.95 |
| 130 | 3-F, 4-N(CH ₃) ₂ | 212-214 | 51.23 | 4.3 | 9.43 | 7.2 | 50.58 | 4.38 | 9.09 | 7.23 |

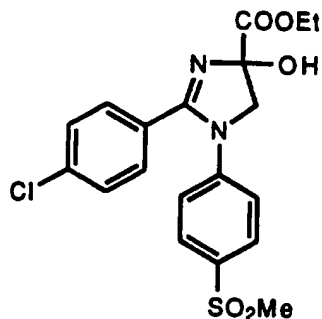
Table IV: Characterization of Compounds



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| Ex. | R | Y | Z | mp DSC (°C) | Elemental Analysis | | | | | | | |
|-----|-----------------|-----------------|----------------------|----------------|--------------------|------|-------|-------|-------|------|-------|-------|
| | | | | | Calc'd | | | | Found | | | |
| | | | | | C | H | N | S | C | H | N | S |
| 131 | NH ₂ | CF ₃ | 3-methoxy-5-pyridyl | 262-264 | 48.24 | 3.29 | 14.06 | 8.05 | 48.49 | 3.34 | 13.55 | 8.01 |
| 132 | CH ₃ | CF ₃ | 3-methoxy-5-pyridyl | 207-208 | 51.38 | 3.55 | 10.57 | 8.07 | 50.98 | 3.31 | 10.38 | 8.15 |
| 133 | CH ₃ | CF ₃ | 2-quinolyl | 264.5 | 57.55 | 3.38 | 10.07 | 7.68 | 57.52 | 3.36 | 9.98 | 7.60 |
| 134 | CH ₃ | CF ₃ | 2-pyrazinyl | 200.6 | 48.91 | 3.01 | 15.21 | | 48.79 | 2.84 | 15.00 | |
| 135 | CH ₃ | CF ₃ | 2-methyl-4-thiazolyl | 197.2 | 46.51 | 3.12 | 10.85 | 16.35 | 46.53 | 3.28 | 10.62 | 16.67 |
| 136 | NH ₂ | H | 5-methyl-2-pyridyl | 216 | 50.26 | 3.43 | 14.65 | | 50.58 | 3.49 | 14.50 | |

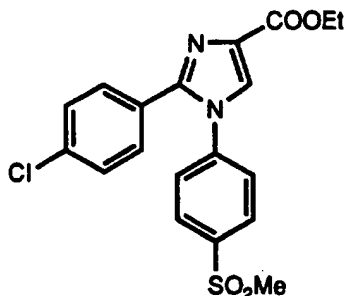
183

Example 137

Ethyl [2-(4-chlorophenyl)-4-hydroxy-1-[4-(methanesulfonyl)phenyl]-4,5-dihydro-1H-imidazol-4-yl] carboxylate

A mixture of 4-chloro-N-[4-(methanesulfonyl)phenyl] benzenecarboximidamide (Example 1, step 1) (1.00 g, 3.34 mmol), sodium bicarbonate (544 mg, 6.47 mmol), and ethyl bromopyruvate (1.40 g, 7.19 mmol) in 50 ml of isopropanol was stirred at reflux for 7 hours. After cooling, the mixture was evaporated. The residue was partitioned between dichloromethane and water, and the aqueous layer further extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue over silica gel using mixtures of ethyl acetate and toluene as eluents gave the title compound as a pale yellow solid: mp (DSC) 162°C. Anal. Calc'd. for C₁₉H₁₉ClN₂O₅S (MW 422.89): C, 53.96; H, 4.53; N, 6.62. Found: C, 53.99; H, 4.49; N, 6.42.

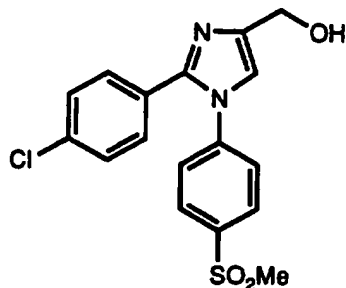
184

Example 138

Ethyl [2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazol-4-yl] carboxylate

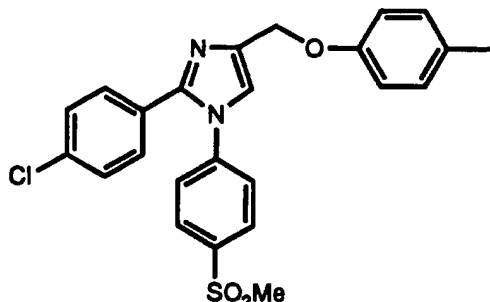
A mixture of 4-chloro-N-[4-(methylsulfonyl)phenyl] benzenecarboximidamide (Example 1, step 1) (12.1 g, 39.2 mmol), sodium bicarbonate (6.58 g, 78.3 mmol), and 90% ethyl bromopyruvate (16.9 g) in 480 ml of 2-propanol was stirred at reflux overnight. After cooling, the mixture was concentrated. The residue was partitioned between dichloromethane and water and the aqueous layer further extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered, and evaporated. Trituration of the residue with ethyl acetate gave the title compound as a pale beige, crystalline solid (6.61 g): mp (DSC) 218°C. Anal. Calc'd. for C₁₉H₁₇ClN₂O₄S (MW 404.87): C, 56.37; H, 4.23; N, 6.92. Found: C, 56.28; H, 4.13; N, 6.80.

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Example 139**2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-
1H-imidazole-4-methanol**

To a solution of 4.00 g (9.88 mmol) of Example 138 in 125 ml of dichloromethane stirring in a dry ice/isopropanol bath was added 24.7 ml of 1M diisobutylaluminum hydride in toluene (containing 24.7 mmol). The mixture was warmed to room temperature overnight. Excess reagent was quenched with methanol, and the resulting mixture was washed with 15% aqueous acetic acid. The aqueous layer was further extracted with dichloromethane, and the combined organic extracts were dried over sodium sulfate. After filtration and evaporation, the residue was triturated with 50% ethyl acetate/hexane, and the alcohol was obtained as a white solid: m.p. 205-208°C. Anal. Calc'd. for C₁₇H₁₅ClN₂O₃S•1/2 H₂O (MW 371.84): C, 54.91; H, 4.07; N, 7.53. Found: C, 54.75; H, 3.96; N, 7.17.

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Example 140**2-(4-Chlorophenyl)-4-[(4-methylphenoxy)methyl]-
1-[4-(methylsulfonyl)phenyl]-1H-imidazole****Step 1: Preparation of 4-chloromethyl-2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole**

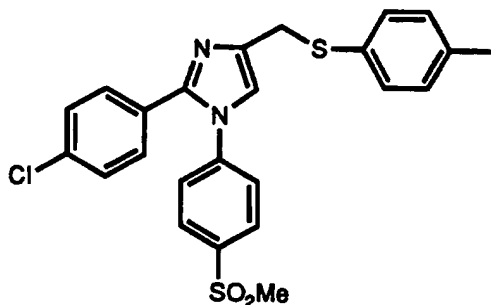
A suspension of the title product of Example 139 (1.82 g, 4.96 mmol) in 10 ml of chloroform was treated with thionyl chloride (1.18 g, 9.92 mmol), and the resulting mixture was stirred at reflux for 1 hour. Another 1.18 g of thionyl chloride was added, and reflux continued for 1 hour. After cooling, the mixture was evaporated and the residue was chromatographed over silica gel using 50% ethyl acetate/hexane as eluent to give the chloromethyl compound as a very pale yellow crystalline solid (1.26 g): m.p. 166-169°C.

Step 2: Preparation of 2-(4-Chlorophenyl)-4-[(4-methylphenoxy)methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

A mixture of 122 mg (0.32 mmole) of 4-chloromethyl-2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (Step 1), p-cresol (69 mg, 0.64 mmole), and potassium carbonate (110 mg, 0.8 mmole) in 5 ml of dimethylformamide was stirred at 85-90 °C for 6 hours. After cooling, the mixture was partitioned between ethyl acetate and aqueous sodium

chloride, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue over silica gel using mixtures of ethyl acetate and hexane gave 2-(4-chlorophenyl)-4-[(4-methylphenoxy)methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole as a pure white solid (118 mg): m.p. (DSC) 193 °C. Anal. Calc'd. for $C_{24}H_{21}ClN_2O_3S$ (MW 452.96): C, 63.64; H, 4.67; N, 6.18. Found: C, 63.42; H, 4.64; N, 5.79.

Example 141



2-(4-Chlorophenyl)-4-[[4-methylphenoxy)thio]methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

To a solution of 4-chloromethyl-2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (Example 140, Step 1) in 5 ml of dimethylformamide was added p-thiocresol (98 mg, 0.79 mmole) and anhydrous potassium carbonate (136 mg, 0.985 mmole), and the mixture was stirred rapidly overnight. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and evaporated. Chromatography of the residue over silica gel using mixtures of ethyl acetate and hexane as eluent gave the title compound as

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a glassy solid: m.p. (DSC) 51 °C. Anal. Calc'd. for $C_{24}H_{21}ClN_2O_2S_2$ (MW 469.03): C, 61.46; H, 4.51; N, 5.97. Found: C, 61.38; H, 4.68; N, 5.81.

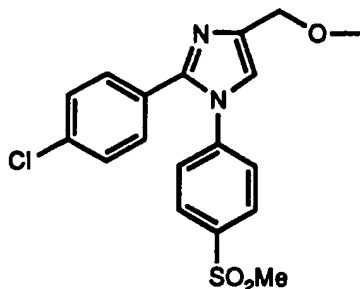
Example 142



2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]- 4-[(4-methylthio)methyl]-1H-imidazole

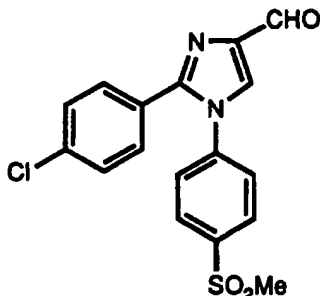
To a solution of 4-chloromethyl-2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (Example 140, Step 1) (150 mg, 0.394 mmole) in 5 ml of dimethylformamide was added sodium thiomethoxide (55 mg, 0.79 mmole) and the mixture was stirred for three days. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue over silica gel using mixtures of ethyl acetate and hexane as eluents gave the title compound as a pale yellow oil (64 mg): Anal. Calc'd. for $C_{18}H_{17}ClN_2O_2S_2 \cdot 1/2 H_2O$ (MW 401.93): C, 53.79; H, 4.26; N, 6.97. Found: C, 53.97; H, 4.43; N, 6.84.

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Example 143**2-(4-Chlorophenyl)-4-(4-methoxymethyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole**

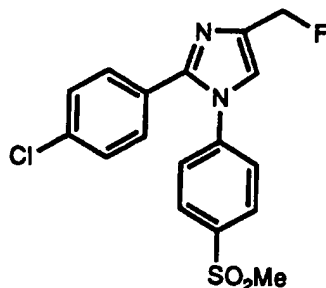
To a solution of 46 mg (2.0 mmol) of sodium metal in 2 ml of methanol was added a solution of 4-chloromethyl-2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (Example 140, Step 1) (167 mg, 0.438 mmole) and the mixture was stirred overnight. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue over silica gel using ethyl acetate as the eluent gave the title compound as a white crystalline solid (72%): mp 171-172 °C. Anal. Calc'd. for $C_{18}H_{17}ClN_2O_3S$ (MW 376.86): C, 57.37; H, 4.55; N, 7.43. Found: C, 57.29; H, 4.42; N, 7.33.

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Example 144**2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-
1H-imidazole-4-carboxaldehyde**

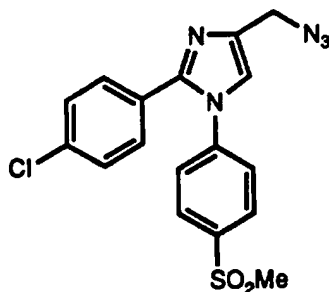
To 8 ml of a 1:1 mixture of dimethyl sulfoxide and dichloromethane stirring in a dry ice/isopropanol bath under nitrogen was added dropwise oxalyl chloride (321 μ l, 3.69 mmol). After stirring for 10 minutes, a solution of 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-methanol (Example 139) (670 mg, 1.85 mmol) in 25 ml of a 1:1 mixture of dimethyl sulfoxide and dichloromethane. Stirring was continued while warming to 0 °C, where it was maintained for 15 minutes. Triethylamine (1.87 g, 18.5 mmol) was added, and the mixture was stirred overnight while warming to room temperature. The mixture was partitioned between dichloromethane and water, the organic layer was washed with water and then brine, dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue over silica gel using mixtures of ethyl acetate and hexane gave the title compound as an off-white solid (330 mg): mp (DSC) 203 °C. Anal. Calc'd. for $C_{17}H_{13}ClN_2O_3S$ (MW 360.82): C, 56.59; H, 3.63; N, 7.76. Found: C, 56.24; H, 3.62; N, 7.50.

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Example 145**2-(4-Chlorophenyl)-4-fluoromethyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole**

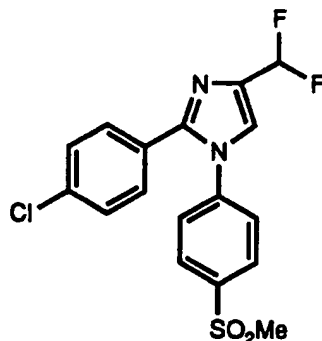
To a suspension of 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-methanol (Example 139) (250 mg, 0.689 mmole) in 5 ml of dichloromethane was added dropwise a solution of diethylamino sulfur trifluoride (DAST) (166 mg, 1.03 mmole) in 1 ml of dichloromethane. As the addition proceeded, the mixture became homogeneous. After stirring for two hours, water was added, the layers separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered and evaporated. Chromatography of the residue over silica gel using 60% ethyl acetate in hexane gave the title compound as a very slightly yellow solid (106 mg): mp (DSC) 165 °C. Anal. Calc'd. for $C_{17}H_{14}ClFN_2O_2S \cdot 1/4 H_2O$ (MW 369.33): C, 55.29; H, 3.82; N, 7.59. Found: C, 55.15; H, 3.82; N, 7.42.

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Example 146**4-Azidomethyl-2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole**

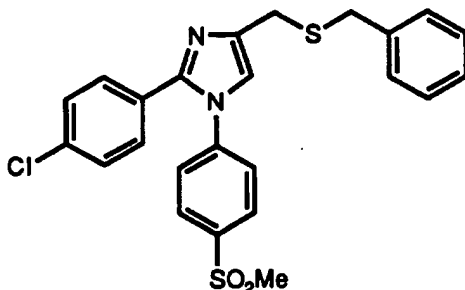
A mixture of 4-chloromethyl-2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (Example 140, Step 1) (500 mg, 1.31 mmol) and sodium azide (256 mg, 3.94 mmol) in 5 ml of dimethylformamide was stirred overnight at room temperature. The mixture was warmed to 80 °C for one hour and then cooled. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue over silica gel using 50% ethyl acetate in hexane as the eluent gave the title compound as a pure white crystalline solid (496 mg): mp (DSC) 186°C. Anal. Calc'd. for C₁₇H₁₄ClN₅O₂S (MW 387.85): C, 52.64; H, 3.64; N, 18.06. Found: C, 52.46; H, 3.77; N, 17.84.

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Example 147**2-(4-Chlorophenyl)-4-difluoromethyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole**

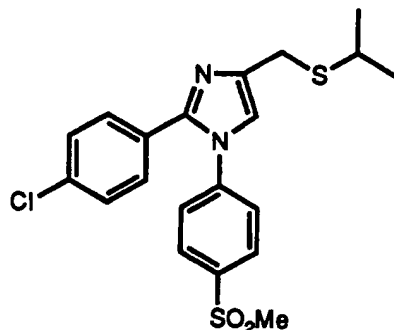
To a suspension of 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-carboxaldehyde (Example 144) (150 mg, 0.416 mmole) in 5 ml of dichloromethane was added dropwise a solution of DAST (201 mg, 1.25 mmol) of in 1 ml of dichloromethane, producing a homogeneous solution. After stirring at room temperature for 30 minutes, the mixture was partitioned between dichloromethane and water, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue over silica gel using 50% ethyl acetate in hexane as the eluent, followed by crystallization from ethyl acetate and hexane gave the title compound as very small pale beige plates (21 mg): m.p. 179-180 °C. Anal. Calc'd. for $C_{17}H_{13}ClF_2N_2O_2S$ (MW 382.82): C, 53.34; H, 3.42; N, 7.32. Found: C, 53.42; H, 3.26; N, 7.08.

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Example 148**2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-
4-[[[(4-phenylmethyl)thio]methyl]-1H-imidazole**

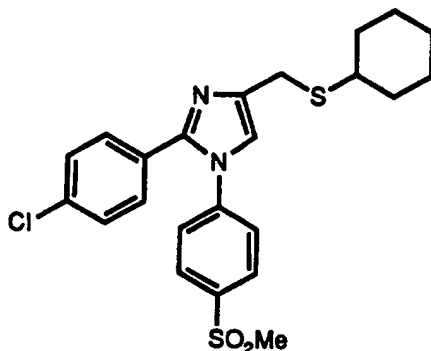
To a solution of benzyl mercaptan (195 mg, 1.6 mmol) in 5 ml of dimethylformamide was added 63 mg of a 60% dispersion of sodium hydride in mineral oil. After gas evolution ceased, 4-chloromethyl-2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (Example 140, Step 1) (300 mg, 0.787 mmole) was added as a solid and stirring continued overnight. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated. Radial chromatography of the residue over a 2 mm layer of silica gel using 50% ethyl acetate in hexane as the eluent gave the title compound as a pale yellow solid (343 mg): mp(DSC) 41°C. Anal. Calc'd. for $C_{24}H_{21}ClN_2O_2S_2$ (MW 469.03): C, 61.46; H, 4.51; N, 5.97. Found: C, 61.06; H, 4.34; N, 5.80.

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Example 149

2-(4-Chlorophenyl)-4-[[[(1-methylethyl)thio]methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

The title compound was prepared as a white solid by the method of Example 148 except that 2-mercaptopropane was used in place of benzyl mercaptan: mp (DSC) 118 °C. Anal. Calc'd. for $C_{20}H_{21}ClN_2O_2S_2$ (MW 420.98): C, 57.06; H, 5.03; N, 6.65. Found: C, 56.72; H, 4.89; N, 6.42.

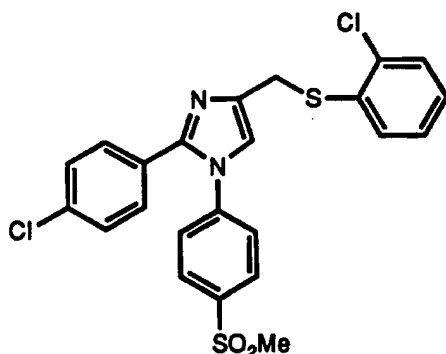
Example 150

2-(4-Chlorophenyl)-4-[[[(cyclohexyl)thio]methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

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The title compound was prepared as a white solid by the method of Example 148 except that cyclohexyl mercaptan was used in place of benzyl mercaptan, and that 40% ethyl acetate in hexane was used as the chromatography eluent: mp (DSC) 48 °C. Anal. Calc'd. for $C_{23}H_{25}ClN_2O_2S_2$ (MW 461.05): C, 59.92; H, 5.47; N, 6.08. Found: C, 59.63; H, 5.52; N, 5.96.

Example 151



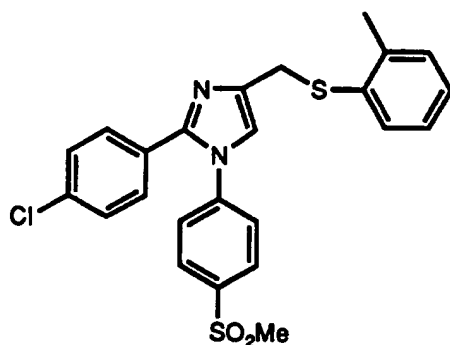
2-(4-Chlorophenyl)-4-[[[2-chlorophenyl]thio]methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

To a solution of 4-chloromethyl-2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (Example 140, Step 1) (250 mg, 0.656 mmol) and 2-chlorothiophenol (190 mg, 1.31 mmol) in 5 ml of dimethylformamide was added potassium carbonate (226 mg, 1.64 mmol). The mixture was stirred rapidly overnight at room temperature and partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, the combined organic extracts were washed with brine, and dried over sodium sulfate. The solution was filtered and then concentrated. Chromatography of the residue over silica gel using 50% ethyl acetate in hexane as the eluent followed by crystallization gave the title

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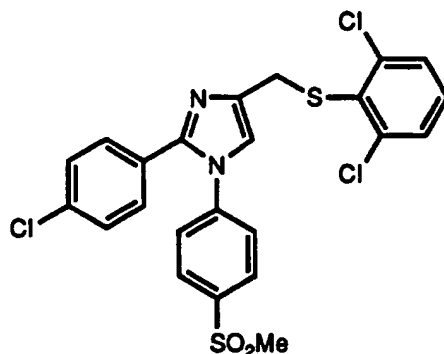
compound as a pure white crystalline solid (147 mg): mp (DSC) 153 °C. Anal. Calc'd. for $C_{23}H_{18}Cl_2N_2O_2S_2$ (MW 489.44): C, 56.44; H, 3.71; N, 5.72. Found: C, 56.51; H, 3.54; N, 5.57.

Example 152



2-(4-Chlorophenyl)-4-[[[2-methylphenyl]thio]methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

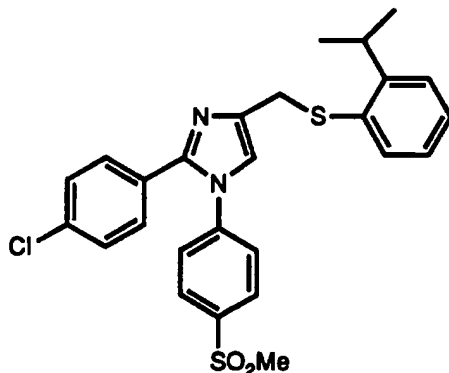
To a solution of 4-chloromethyl-2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (Example 140, Step 1) (250 mg, 0.656 mmol) and o-thiocresol (163 mg, 1.31 mmol) in 5 ml of dry dimethylformamide was added anhydrous potassium carbonate (226 mg, 1.64 mmol). The mixture was stirred rapidly overnight at room temperature. The mixture was then partitioned between ethyl acetate and water. The aqueous layer was further extracted with ethyl acetate, the combined organic extracts washed with brine, and dried over sodium sulfate. The solution was filtered and concentrated. Chromatography of the residue over silica gel using 40% ethyl acetate in hexane gave the title compound as a very pale yellow solid (210 mg): mp (DSC) 51 °C. Anal. Calc'd. for $C_{24}H_{21}ClN_2O_2S_2$ (MW 469.03): C, 61.46; H, 4.51; N, 5.97. Found: C, 61.16; H, 4.50; N, 5.86.

Example 153

2-(4-Chlorophenyl)-4-[[2,6-dichlorophenylthio]methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

To a solution of 4-chloromethyl-2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (Example 140, Step 1) (250 mg, 0.656 mmole) and 2,6-dichlorothiophenol in 5 ml of dimethylformamide (235 mg, 1.31 mmol) was added 226 mg (1.64 mmol) of potassium carbonate. The resulting mixture was stirred rapidly at room temperature for two days. The mixture was partitioned between ethyl acetate and water and the aqueous layer was further extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue over silica gel using 50% ethyl acetate in hexane gave the title compound, 282 mg, as a pure white solid: mp (DSC) 202 °C. Anal. Calc'd. for C₂₃H₁₇Cl₃N₂O₂S₂ (MW 523.89): C, 52.73; H, 3.27; N, 5.35. Found: C, 52.55; H, 2.98; N, 5.19.

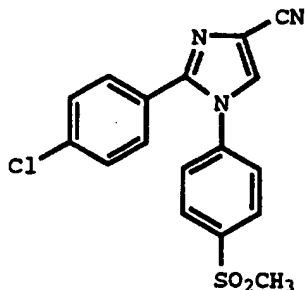
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Example 154

2-(4-Chlorophenyl)-4-[[[2-(1-methylethyl)phenyl]thio]methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

The title compound was prepared as a white solid by the method of Example 153 except that 2-isopropylthiophenol was used in place of 2,6-dichlorothiophenol and that 40% ethyl acetate in hexane was used as chromatography eluent: m.p. 68-70 °C.

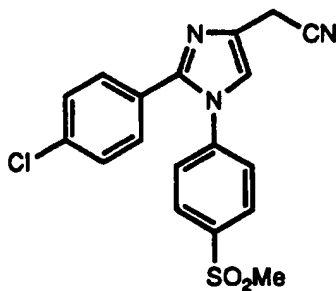
Anal. Calc'd. for $C_{26}H_{25}ClN_2O_2S_2 \cdot 1/4H_2O$ (MW 501.58): C, 62.26; H, 5.02; N, 5.59. Found: C, 62.36; H, 5.11; N, 5.45.

Example 155

2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-carbonitrile

A solution of 82 mg (0.23 mmole) of 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-carboxaldehyde (Example 144) and 51 mg (0.45 mmole) of hydroxylamine O-sulfonic acid in 10 ml of absolute ethanol and 1 ml of pyridine was stirred at reflux overnight. After cooling, the mixture was evaporated, and the residue was taken up in dichloromethane. The solution was washed with aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue over silica gel using 50% ethyl acetate in hexane as the eluent gave the title compound, 71 mg, as a pure white crystalline solid: mp (DSC) 205 °C. Anal. Calc'd. for $C_{17}H_{12}ClN_3O_2S \cdot 1/4 H_2O$ (MW 362.32): C, 56.36; H, 3.34; N, 11.60. Found: C, 56.49; H, 3.27; N, 11.45.

Example 156



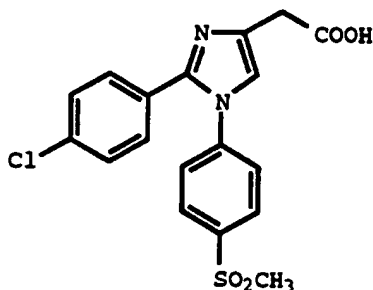
2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-acetonitrile

A mixture of 250 mg (0.656 mmole) of 4-chloromethyl-2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (Example 140, Step 1) and 86 mg (1.3 mmol) of potassium cyanide in 4 ml of dimethylformamide was stirred at 85 °C for 24 hours. An additional 86 mg of potassium cyanide was added, and

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stirring continued for 8 hours. After cooling, the mixture was partitioned between dichloromethane and water and the aqueous layer further extracted with dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue over silica gel using 60% ethyl acetate in toluene, followed by trituration with ethyl acetate gave the title compound, 59 mg, as a very pale yellow crystalline solid: mp (DSC) 197 °C. Anal. Calc'd. for $C_{18}H_{14}ClN_3O_2S$ (MW 371.85): C, 58.14; H, 3.80; N, 11.30. Found: C, 57.92; H, 3.57; N, 11.01.

Example 157

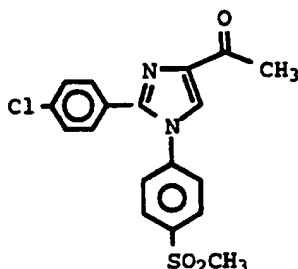


2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]- 1H-imidazole-4-acetic acid

A mixture of 50 mg (0.13 mmole) of the title product of Example 156 and 5 ml of concentrated hydrochloric acid was stirred at reflux for one hour. After cooling, the mixture was evaporated and the residue taken up in water. The mixture was basified with aqueous sodium bicarbonate solution, and the pH then adjusted to 4 with acetic acid. The mixture was extracted with dichloromethane and the combined organic extracts dried over sodium sulfate. After filtration, the solution was evaporated and the residue azeotropically distilled with toluene. Trituration of

the residue with ethyl acetate gave the title compound, 31 mg, as a white solid: m.p. 263-264 °C. Anal. Calc'd. for $C_{18}H_{15}ClN_2O_4S \cdot 1/4H_2O$ (MW 395.35): C, 54.69; H, 3.82; N, 7.09. Found: C, 54.39; H, 3.88; N, 6.72.

Example 158



1-[2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazol-4-yl]-1-ethanone

Step 1- Preparation of 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-carboxylic acid

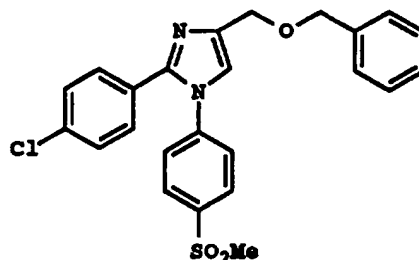
A suspension of ethyl [2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazol-4-yl] carboxylate (Example 138) (929 mg, 2.29 mmol) in 16 ml of methanol and 16 ml of 1N aqueous sodium hydroxide was stirred at reflux for one hour. After cooling, the mixture was concentrated, water was added, and the resulting mixture was acidified with acetic acid. The mixture was extracted with dichloromethane, and the combined organic extracts were dried over sodium sulfate, filtered, and evaporated. Acetic acid was removed by azeotropic distillation with toluene to give the title compound, 520 mg, as a white crystalline solid: mp (DSC) 121 °C. Anal. Calc'd. for $C_{17}H_{13}ClN_2O_4S \cdot H_2O$ (MW 394.83): C, 51.71; H, 3.32; N, 7.10. Found: C, 51.89; H, 3.29; N, 6.97.

Step 2 - Preparation of 2-(4-chlorophenyl)-N-methoxy-N-methyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-carboxamide

Oxalyl chloride (0.34 g, 2.65 mmole) in 5 ml acetonitrile was added to 16 ml acetonitrile containing dimethylformamide (0.25 g, 3.46 mmole) cooled to 0°C. After 15 minutes, 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-carboxylic acid from step 1 (1.0 g, 2.65 mmole) was added with 20 ml acetonitrile. After warming to room temperature N,O-dimethylhydroxylamine HCl (0.28 g, 2.92 mmole) and pyridine (0.42 g, 5.31 mmole) were added and the mixture was stirred at room temperature for three days. The reaction mixture was concentrated to give an oily solid. The amide was purified by silica gel chromatography: Anal. Calc'd. $C_{19}H_{18}N_3O_4SCl$ (419.89); C, 54.35; H, 4.32; N, 10.01. Found: C, 53.96; H, 4.30; N, 9.68.

Step 3 - Preparation of 1-[2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-yl]-1-ethanone

Methyl lithium-LiBr complex (1.5 M in ethyl ether) (0.47 ml, 0.7 mmol) was added by syringe to a cold (-70°C) solution of 2-(4-chlorophenyl)-N-methoxy-N-methyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole-4-carboxamide from step 2 (250 mg, 0.6 mmol) in 50 ml tetrahydrofuran. The reaction was warmed to 0°C and re-cooled to -60°C before additional methyl lithium (0.47 ml) was added. The reaction was warmed to room temperature. After stirring for two days, 50 ml of 10% acetic acid was added and the mixture was concentrated to a gum. The gum was dissolved in 50 ml ethyl acetate, washed with water (2 x 50 ml), dried over Na_2SO_4 , filtered and concentrated. The product was purified by silica gel chromatography: Anal. Calc'd. $C_{18}H_{15}N_2O_3SCl \cdot 1/4 H_2O$: C, 56.99; H, 4.12; N, 7.38. Found: C, 56.88; H, 4.05; N, 7.6838

Example 159**2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-
4-(benzylmethoxymethyl)-1H-imidazole**

To a suspension of 58 mg of 60% sodium hydride in mineral oil (containing 35 mg, 1.4 mmol) in 2 ml of dimethylformamide was added a solution of 142 mg (1.31 mmol) of benzyl alcohol in 0.5 ml of dimethylformamide. The mixture was stirred while heating to 40°C. After 15 minutes, 250 mg (0.656 mmole) of the title product of Example 139 was added as a solid and stirred while heating to 85°C. The temperature was maintained for 6 hours and then the mixture was cooled. The mixture was partitioned between ethyl acetate and water and the aqueous layer further extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue over silica gel using 50% ethyl acetate in hexane as the eluent gave the title compound, 60 mg, as pure white crystalline solid, m.p. 64-65°C. Anal. Calc'd. for $C_{24}H_{21}ClN_2O_3S \cdot 1/4H_2O$ (MW 457.56): C, 63.01; H, 4.63; N, 6.12. Found: C, 62.76; H, 4.43; N, 6.20.

BIOLOGICAL EVALUATION**Rat Carrageenan Foot Pad Edema Test**

The carrageenan foot edema test was performed with materials, reagents and procedures essentially as described by Winter, et al., (*Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962)). Male Sprague-Dawley rats were selected in each group so that the average body weight was as close as possible. Rats were fasted with free access to water for over sixteen hours prior to the test. The rats were dosed orally (1 ml) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later a subplantar injection of 0.1 ml of 1% solution of carrageenan/sterile 0.9% saline was administered and the volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a group of drug-treated animals was compared with that of a group of placebo-treated animals and the percentage inhibition of edema was determined (Otterness and Bliven, *Laboratory Models for Testing NSAIDs*, in *Non-steroidal Anti-Inflammatory Drugs*, (J. Lombardino, ed. 1985)). The % inhibition shows the % decrease from control paw volume determined in this procedure and the data for selected compounds in this invention are summarized in Table V.

Rat Carrageenan-induced Analgesia Test

The rat carrageenan analgesia test was performed with materials, reagents and procedures essentially as described by Hargreaves, et al., (*Pain*, 32, 77 (1988)). Male Sprague-Dawley rats were treated as previously described for the Carrageenan Foot Pad Edema test.

Three hours after the injection of the carrageenan, the rats were placed in a special plexiglass container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty minute period, thermal stimulation was begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell turned off the lamp and timer when light was interrupted by paw withdrawal. The time until the rat withdraws its foot was then measured. The withdrawal latency in seconds was determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal determined. Results are shown in Table V.

TABLE V.

| | RAT PAW EDEMA | | ANALGESIA | |
|---------|-----------------------|------|-----------------------|----|
| | % Inhibition | | % Inhibition | |
| | @ 30mg/kg body weight | | @ 10mg/kg body weight | |
| Example | | | | |
| 2 | | 9 | | |
| 5 | | 21 | | |
| 6 | | 23.5 | | |
| 7 | | 27 | | |
| 18 | | 36 | | 13 |
| 23 | | 38 | | 25 |
| 24 | | 24 | | 19 |
| 26 | | 51 | | 47 |
| 27 | | 40 | | 21 |
| 28 | | 57 | | 51 |
| 29 | | 37 | | |
| 31 | | 28 | | 36 |
| 32 | | 30 | | |
| 36 | | 68 | | |
| 40 | | 42 | | |
| 43 | | 45* | | 18 |
| 45 | | 49 | | 47 |

TABLE V. (cont.)

| | RAT PAW EDEMA | | ANALGESIA | |
|------------|-----------------------|-----|-----------------------|----|
| | % Inhibition | | % Inhibition | |
| | @ 30mg/kg body weight | | @ 10mg/kg body weight | |
| Example | | | | |
| 59 | | 34 | | 27 |
| 69 | | 43 | | 32 |
| 70 | | 34* | | 35 |
| 72 | | 55 | | 28 |
| 74 | | 48 | | |
| 83 | | 25 | | |
| 84a | | 36 | | 8 |
| 86 | | 36 | | 7 |
| 87 | | 28* | | 5 |
| 91 | | 16 | | |
| 93 | | 16 | | 4 |
| 117 | | 51 | | |
| * 10 mg/kg | | | | |

Evaluation of COX-1 and COX-2 activity *in vitro*

The compounds of this invention exhibited inhibition *in vitro* of COX-2. The COX-2 inhibition activity of the compounds of this invention illustrated in the Examples was determined by the following methods.

a. Preparation of recombinant COX baculoviruses

Recombinant COX-1 and COX-2 were prepared as described by Gierse et al, [*J. Biochem.*, 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 was cloned into a BamHI site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R.

O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses were isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells (2×10^8) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses were purified by three rounds of plaque purification and high titer (10^7 - 10^8 pfu/ml) stocks of virus were prepared. For large scale production, SF9 insect cells were infected in 10 liter fermentors (0.5×10^6 /ml) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate was centrifuged at 10,000xG for 30 minutes, and the resultant supernatant was stored at -80°C before being assayed for COX activity.

b. Assay for COX-1 and COX-2 activity

COX activity was assayed as PGE₂ formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme were incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 µM). Compounds were pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after ten minutes at 37°C/room temperature by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE₂ formed was measured by standard

ELISA technology (Cayman Chemical). Results are shown in Table VI.

TABLE VI.

| Example | Human COX-2 | Human COX-1 |
|---------|--------------------------|--------------------------|
| | ID ₅₀ μ M | ID ₅₀ μ M |
| 1 | 4 | >100 |
| 2 | 0.1 | 23 |
| 3 | 40 | >100 |
| 4 | 4.7 | >100 |
| 5 | 0.2 | >100 |
| 6 | 0.3 | >100 |
| 7 | 0.1 | >100 |
| 9 | 0.3 | >100 |
| 10 | 0.5 | >100 |
| 12 | 0.2 | >100 |
| 13 | 1.6 | >100 |
| 14 | 0.2 | >100 |
| 16 | <0.1 | >100 |
| 17 | 0.2 | 1.0 |
| 18 | 0.2 | 49 |
| 23 | 0.1 | >100 |
| 24 | 0.2 | 26 |
| 26 | <0.1 | 1.6 |
| 27 | <0.1 | 0.6 |
| 28 | 1.8 | >100 |
| 29 | 1.5 | >100 |
| 30 | >100 | >100 |
| 31 | 1.8 | >100 |
| 32 | 2.9 | >100 |
| 34 | 0.5 | >100 |
| 35 | 1.2 | 49 |
| 36 | 0.3 | 88.5 |
| 40 | 0.4 | >100 |
| 41 | 0.5 | >100 |
| 43 | 0.5 | >100 |
| 45 | 9.6 | >100 |

TABLE VI. (cont.)

| Example | Human COX-2 | Human COX-1 |
|---------|--------------------------|--------------------------|
| | ID ₅₀ μ M | ID ₅₀ μ M |
| 56 | 0.1 | 3.6 |
| 57 | <0.1 | 0.9 |
| 59 | <0.1 | 3.6 |
| 67 | 1.1 | >100 |
| 68 | 0.2 | 4.6 |
| 69 | <0.1 | 2.8 |
| 70 | <0.1 | 6.2 |
| 72 | <0.1 | 19.3 |
| 73 | <0.1 | 29.8 |
| 74 | <0.1 | 5.8 |
| 75 | <0.1 | 67.7 |
| 76 | <0.1 | 8.6 |
| 78 | <0.1 | 2.7 |
| 79 | 0.1 | 31.2 |
| 80 | <0.1 | 7.0 |
| 81 | <0.1 | 3.6 |
| 82 | <0.1 | >100 |
| 83 | <0.1 | 82.0 |
| 85 | 0.1 | >100 |
| 86 | <0.1 | 78.1 |
| 87 | <0.1 | >100 |
| 88 | <0.1 | >100 |
| 89 | 0.2 | 24.1 |
| 90 | 0.2 | >100 |
| 91 | 0.2 | >100 |
| 93 | 0.1 | >100 |
| 94 | 0.2 | 29.9 |
| 95 | 0.6 | 3.0 |
| 96 | 0.4 | >100 |
| 97 | 0.3 | >100 |
| 98 | 1.0 | >100 |
| 99 | 0.2 | 2.1 |

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TABLE VI. (cont.)

| Example | Human COX-2 | Human COX-1 |
|---------|--------------------------|--------------------------|
| | ID ₅₀ μ M | ID ₅₀ μ M |
| 101 | 0.7 | >100 |
| 103 | 0.5 | >100 |
| 104 | 0.9 | >100 |
| 105 | 0.8 | 4.5 |
| 106 | 0.3 | 17.1 |
| 107 | <0.1 | >100 |
| 108 | 0.6 | >100 |
| 109 | 1.48 | 53.5 |
| 112 | 0.7 | >100 |
| 113 | 0.3 | >100 |
| 114 | <0.1 | >100 |
| 115 | 0.1 | >100 |
| 116 | 0.1 | >100 |
| 117 | 0.1 | >100 |
| 118 | <0.1 | 7.9 |
| 119 | 0.3 | 1.6 |
| 120 | <0.1 | >100 |
| 140 | <0.1 | >100 |
| 141 | <0.1 | >100 |
| 142 | 0.6 | >100 |
| 144 | 1.6 | >100 |
| 145 | 0.4 | >100 |
| 147 | 0.6 | >100 |
| 148 | 0.1 | >100 |
| 149 | 0.6 | >100 |
| 150 | 0.1 | >100 |
| 151 | <0.1 | >100 |
| 152 | <0.1 | >100 |
| 153 | <0.1 | 13.7 |
| 154 | <0.1 | >100 |
| 155 | 0.3 | >100 |
| 156 | 1.5 | >100 |
| 159 | 0.5 | 100 |

Biological paradigms for testing the cytokine-inhibiting activity of these compounds are found in WO95/13067, published 18 May 1995.

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of this combination therapy in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and composition may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between

about 0.5 and about 20 mg/kg body weight and most preferably between about 0.1 to 10 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

For inflammations of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to

the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

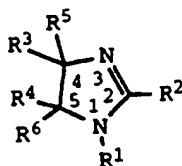
Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The antiinflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What is claimed is:

1. A compound of Formula I



(I)

5

wherein R¹ and R² are independently selected from aryl, cycloalkyl, cycloalkenyl and heterocyclo, wherein R¹ and R² are optionally substituted at a substitutable position with one or more radicals independently selected from alkylsulfonyl, aminosulfonyl, haloalkylsulfonyl, halo, alkylthio, alkyl, cyano, carboxyl, alkoxycarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, alkoxyalkyl, haloalkoxy, amino, alkylamino, arylamino and nitro;

15 wherein R³ is a radical selected from hydrido, alkyl, haloalkyl, aralkyl, heterocycloalkyl, acyl, cyano, alkoxy, alkylthio, alkylthioalkyl, alkylsulfonyl, cycloalkylthio, cycloalkylthioalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, cycloalkyloxy, cycloalkyloxyalkyl, haloalkylsulfonyl, arylsulfonyl, halo, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocycloalkylcarbonyl, cyanoalkyl, azidoalkyl, aminoalkyl, alkylaminoalkyl, N-aryl aminoalkyl, N-alkyl-N-aryl aminoalkyl, carboxyalkyl, 20 alkoxy carbonylalkyl, alkoxy carbonyl, haloalkylcarbonyl, carboxyl, aminocarbonyl, alkylaminocarbonyl, alkylaminocarbonylalkyl, heteroarylalkoxyalkyl, heteroarylloxyalkyl, heteroarylthioalkyl, aralkoxy, aralkylthio, heteroaralkoxy, heteroaralkylthio, heteroarylalkylthioalkyl, heteroarylloxy, heteroarylthio, arylthioalkyl, aryloxyalkyl, arylthio, aryloxy, aralkylthioalkyl, aralkoxyalkyl, aryl and heterocyclo;

wherein R⁴ is a radical selected from hydrido, alkyl and fluoro;

30

wherein R⁵ is selected from hydroxyl and alkoxy;
and

wherein R⁶ is hydrido; or wherein R⁵ and R⁶
together form a double bond;

5 provided at least one of R¹ and R² is aryl
substituted with alkylsulfonyl, haloalkylsulfonyl or
aminosulfonyl;

or a pharmaceutically-acceptable salt thereof.

2. Compound of Claim 1 wherein R¹ and R² are
10 independently selected from phenyl, naphthyl, biphenyl,
lower cycloalkyl, lower cycloalkenyl and heteroaryl,
wherein R¹ and R² are optionally substituted at a
substitutable position with one or more radicals
independently selected from lower alkylsulfonyl,
15 aminosulfonyl, lower haloalkylsulfonyl, halo, lower
alkylthio, lower alkyl, cyano, carboxyl, lower
alkoxycarbonyl, lower haloalkyl, hydroxyl, lower alkoxy,
lower hydroxyalkyl, lower alkoxyalkyl, lower haloalkoxy,
amino, lower alkylamino, arylamino and nitro; wherein R³
20 is a radical selected from hydrido, lower alkyl, lower
haloalkyl, lower aralkyl, lower heterocycloalkyl, acyl,
cyano, lower alkoxy, lower alkylthio, lower
alkylsulfonyl, lower cycloalkyloxy, lower
cycloalkyloxyalkyl, lower cycloalkylthio, lower
25 cycloalkylthioalkyl, lower cycloalkylsulfonyl, lower
cycloalkylsulfonylalkyl, phenylsulfonyl, lower
haloalkylsulfonyl, halo, lower hydroxyalkyl, lower
alkoxyalkyl, lower alkylcarbonyl, lower azidoalkyl,
lower haloalkylcarbonyl, phenylcarbonyl, lower
30 aralkylcarbonyl, lower heterocycloalkylcarbonyl, lower
cyanoalkyl, lower aminoalkyl, lower alkylaminoalkyl,
lower N-arylaminomethyl, lower N-alkyl-N-arylaminomethyl,
lower carboxyalkyl, lower alkoxyalkyl, lower
alkoxyalkyl, lower alkylthioalkyl, aminocarbonyl,
35 lower alkylaminocarbonyl, lower alkylaminocarbonylalkyl,
lower aralkoxy, lower aralkylthio, lower heteroaralkoxy,
lower heteroaralkylthio, lower heteroarylalkoxyalkyl,

lower heteroarylalkylthioalkyl, lower
heteroaryloxyalkyl, lower heteroarylthioalkyl, lower
heteroaryloxy, lower heteroarylthio, lower
arylthioalkyl, lower aryloxyalkyl, lower arylthio, lower
5 aryloxy, lower aralkylthioalkyl, lower aralkoxyalkyl,
aryl selected from phenyl and naphthyl, and heteroaryl,
wherein the aryl and heteroaryl radicals are optionally
substituted at a substitutable position with one or more
radicals selected from halo, lower alkylthio, lower
10 alkylsulfinyl, lower alkyl, cyano, lower haloalkyl,
hydroxyl, lower alkoxy, lower hydroxyalkyl and lower
haloalkoxy; wherein R⁴ is a radical selected from
hydrido, lower alkyl and fluoro; and wherein R⁵ is
selected from hydroxyl and lower alkoxy; wherein R⁶ is
15 hydrido; or wherein R⁵ and R⁶ together form a double
bond; or a pharmaceutically-acceptable salt thereof.

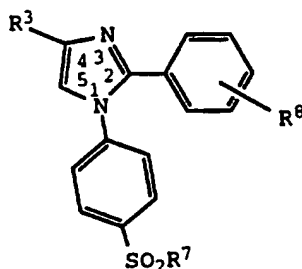
3. Compound of Claim 2 wherein R¹ and R² are
independently selected from phenyl, naphthyl, biphenyl,
cyclohexyl, cyclohexenyl, benzofuryl, benzodioxolyl,
20 furyl, imidazolyl, thienyl, thiazolyl, pyrrolyl,
oxazolyl, isoxazolyl, triazolyl, pyrimidinyl,
quinolinyl, benzimidazolyl, indolyl, pyrazolyl and
pyridyl, wherein R¹ and R² are optionally substituted at
a substitutable position with one or more radicals
25 independently selected from methylsulfonyl,
aminosulfonyl, fluoromethylsulfonyl,
difluoromethylsulfonyl, fluoro, chloro, bromo,
methylthio, methyl, ethyl, isopropyl, tert-butyl,
isobutyl, pentyl, hexyl, cyano, carboxyl,
30 methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl,
tert-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl,
isobutoxycarbonyl, pentoxycarbonyl, fluoromethyl,
difluoromethyl, trifluoromethyl, chloromethyl,
dichloromethyl, trichloromethyl, pentafluoroethyl,
35 heptafluoropropyl, difluorochloromethyl,
dichlorofluoromethyl, difluoroethyl, difluoropropyl,
dichloroethyl, dichloropropyl, hydroxyl, methoxy,

- methylenedioxy, ethoxy, propoxy, n-butoxy, hydroxymethyl, hydroxyethyl, methoxymethyl, ethoxymethyl, trifluoromethoxy, amino, methylamino, N,N-dimethylamino, phenylamino and nitro; wherein R³ is a
- 5 radical selected from hydrido, methyl, ethyl, isopropyl, tert-butyl, isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl,
- 10 dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, benzyl, phenylethyl, phenylpropyl, furylmethyl, morpholinomethyl, pyrrolidinylmethyl, piperazinylmethyl, piperidinylmethyl, pyridylmethyl, thienylmethyl, formyl,
- 15 cyano, methoxy, ethoxy, propoxy, n-butoxy, methylthio, ethylthio, isopropylthio, methylsulfonyl, phenylsulfonyl, trifluoromethylsulfonyl, fluoro, chloro, bromo, hydroxymethyl, hydroxyethyl, methoxymethyl, ethoxymethyl, methylthiomethyl, isopropylthiomethyl,
- 20 cyclohexylthiomethyl, benzyloxy, benzylthio, methylcarbonyl, ethylcarbonyl, phenylcarbonyl, azidomethyl, trifluoromethylcarbonyl, difluoromethylcarbonyl, fluoromethylcarbonyl, benzylcarbonyl, cyanomethyl, cyanobutyl, aminomethyl,
- 25 methylaminomethyl, N-phenylaminomethyl, N-methyl-N-phenylaminomethyl, acetyl, propanoyl, butanoyl, methoxycarbonylmethyl, ethoxycarbonylethyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, propoxycarbonyl, isobutoxycarbonyl,
- 30 carboxymethyl, carboxypropyl, aminocarbonyl, methylaminocarbonyl, N,N-diethylaminocarbonyl, N-methylaminocarbonylmethyl, pyridyloxy, pyridylthio, phenyloxy, 4-chlorophenoxy, furylmethoxy, furylmethylthio, 5-phenylpyridyl-2-methoxy,
- 35 thienylmethoxy, quinolylmethoxy, pyridylmethoxy, thienylmethylthio, pyridylmethylthio, benzylthiomethyl, quinolylmethoxymethyl, furylbutoxyethyl,

pyridyloxymethyl, pyridylmethoxymethyl, thienyloxyhexyl, thienylthiomethyl, pyridylthiohexyl, furyloxymethyl, furylmethylthiomethyl, quinolylmethylthioethyl, phenylthiomethyl, 2-chlorophenylthiomethyl, 2,6-
 5 dichlorophenylthiomethyl, 4-methylphenylthiomethyl, 2-isopropylphenylthiomethyl, 2-methylphenylthiomethyl, phenyloxymethyl, 4-chlorophenyloxymethyl, 4-methylphenyloxymethyl, benzyloxymethyl, 4-methoxybenzyloxymethyl, naphthyl, phenyl, thienyl,
 10 furyl, pyridyl, wherein the thienyl, furyl, pyridyl and phenyl radicals are optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methylsulfinyl, methyl, ethyl, isopropyl, tert-butyl,
 15 isobutyl, pentyl, hexyl, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl,
 20 dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, hydroxymethyl, hydroxyethyl and trifluoromethoxy; wherein R^4 is a radical selected from hydrido, methyl, ethyl, and fluoro; and wherein R^5 is selected from
 25 hydroxyl, methoxy, ethoxy, propoxy and n-butoxy; wherein R^6 is hydrido; or wherein R^5 and R^6 together form a double bond; or a pharmaceutically-acceptable salt thereof.

4. A compound of Formula II

30



(II)

- wherein R^3 is a radical selected from hydrido, alkyl, haloalkyl, aralkyl, heterocycloalkyl, acyl, cyano, alkoxy, alkylthio, alkylthioalkyl, alkylsulfonyl, cycloalkyloxy, cycloalkyloxyalkyl, cycloalkylthio, cycloalkylthioalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, haloalkylsulfonyl, arylsulfonyl, halo, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocycloalkylcarbonyl, cyanoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-alkyl-N-arylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, haloalkylcarbonyl, aminocarbonyl, azidoalkyl, alkylaminocarbonylalkyl, heteroarylalkoxyalkyl, heteroaryloxyalkyl, heteroarylthioalkyl, aralkoxy, aralkylthio, heteroaralkoxy, heteroaralkylthio, heteroarylalkylthioalkyl, heteroaryloxy, heteroarylthio, arylthioalkyl, aryloxyalkyl, arylthio, aryloxy, aralkylthioalkyl, aralkoxyalkyl, aryl and heteroaryl, wherein the aryl and heteroaryl radicals are optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkyl, cyano, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl and haloalkoxy; wherein R^7 is a radical selected from alkyl, and amino; and wherein R^8 is one or more radicals selected from hydrido, halo, alkyl, haloalkyl, alkoxy, amino, haloalkoxy, cyano, carboxyl, hydroxyl, hydroxyalkyl, alkoxyalkyl, alkylamino, nitro and alkylthio; or a pharmaceutically-acceptable salt thereof.
5. Compound of Claim 4 wherein R^3 is a radical selected from hydrido, lower alkyl, lower haloalkyl, lower aralkyl, lower heterocycloalkyl, acyl, cyano, lower alkoxy, lower alkylthio, lower alkylsulfonyl, phenylsulfonyl, lower haloalkylsulfonyl, lower cycloalkyloxy, lower cycloalkyloxyalkyl, lower cycloalkylthio, lower cycloalkylthioalkyl, lower cycloalkylsulfonyl, lower cycloalkylsulfonylalkyl, halo,

- lower hydroxyalkyl, lower alkoxyalkyl, lower alkylcarbonyl, lower haloalkylcarbonyl, phenylcarbonyl, lower aralkylcarbonyl, lower heterocycloalkylcarbonyl, lower cyanoalkyl, lower azidoalkyl, lower
- 5 alkylaminoalkyl, lower N-arylaminoalkyl, lower N-alkyl-N-arylaminoalkyl, lower carboxyalkyl, lower alkoxycarbonylalkyl, lower alkoxycarbonyl, lower alkylthioalkyl, aminocarbonyl, lower alkylaminocarbonylalkyl, lower aralkoxy, lower
- 10 aralkylthio, lower heteroaralkoxy, lower heteroaralkylthio, lower heteroarylalkoxyalkyl, lower heteroarylalkylthioalkyl, lower heteroaryloxyalkyl, lower heteroarylthioalkyl, lower heteroaryloxy, lower heteroarylthio, lower arylthioalkyl, lower aryloxyalkyl,
- 15 lower arylthio, lower aryloxy, lower aralkylthioalkyl, lower aralkoxyalkyl, aryl selected from phenyl and naphthyl, 5 or 6 membered heteroaryl, wherein the aryl and heteroaryl radicals are optionally substituted at a substitutable position with one or more radicals
- 20 selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, cyano, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl and lower haloalkoxy; wherein R^7 is a radical selected from lower alkyl, and amino; and wherein R^8 is a radical selected
- 25 from hydrido, halo, lower alkyl, lower haloalkyl, lower alkoxy, amino, lower haloalkoxy, cyano, carboxyl, hydroxyl, lower hydroxyalkyl, lower alkoxyalkyl, lower alkylamino, nitro and lower alkylthio; or a pharmaceutically-acceptable salt thereof.
- 30 6. Compound of Claim 5 wherein R^3 is a radical selected from hydrido, methyl, ethyl, isopropyl, tert-butyl, isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl,
- 35 heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, benzyl, phenylethyl,

- phenylpropyl, furylmethyl, morpholinomethyl,
pyrrolidinylmethyl, piperazinylmethyl,
piperidinylmethyl, pyridylmethyl, thienylmethyl, formyl,
cyano, methoxy, ethoxy, propoxy, n-butoxy, methylthio,
5 ethylthio, isopropylthio, methylsulfonyl,
phenylsulfonyl, trifluoromethylsulfonyl, fluoro, chloro,
bromo, hydroxymethyl, hydroxyethyl, methoxymethyl,
ethoxymethyl, methylthiomethyl, isopropylthiomethyl,
cyclohexylthiomethyl, benzyloxy, benzylthio,
10 methylcarbonyl, phenylcarbonyl, trifluoromethylcarbonyl,
difluoromethylcarbonyl, fluoromethylcarbonyl,
benzylcarbonyl, cyanomethyl, cyanobutyl, azidomethyl,
methylaminomethyl, N-phenylaminomethyl, N-methyl-N-
phenylaminomethyl, acetyl, propanoyl, butanoyl,
15 methoxycarbonylmethyl, ethoxycarbonylethyl,
methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl,
tert-butoxycarbonyl, propoxycarbonyl, carboxymethyl,
carboxypropyl, aminocarbonyl, N-
methylaminocarbonylmethyl, pyridyloxy, pyridylthio,
20 phenyloxy, 4-chlorophenoxy, furylmethoxy, 5-
phenylpyridyl-2-methoxy, furylmethylthio,
thienylmethoxy, quinolylmethoxy, pyridylmethoxy,
thienylmethylthio, pyridylmethylthio, benzylthiomethyl,
quinolylmethoxymethyl, furylbutoxyethyl,
25 pyridyloxymethyl, pyridylmethoxymethyl, thienyloxyhexyl,
thienylthiomethyl, pyridylthiohexyl, furyloxymethyl,
furylmethylthiomethyl, quinolylmethylthioethyl,
phenylthiomethyl, 2-chlorophenylthiomethyl, 2,6-
dichlorophenylthiomethyl, 4-methylphenylthiomethyl, 2-
30 isopropylphenylthiomethyl, 2-methylphenylthiomethyl,
phenyloxymethyl, 4-chlorophenyloxymethyl, 4-
methylphenyloxymethyl, benzyloxymethyl, 4-
methoxybenzyloxymethyl, naphthyl, phenyl, thienyl,
furyl, pyridyl, wherein the thienyl, furyl, pyridyl and
35 phenyl radicals are optionally substituted at a
substitutable position with one or more radicals
selected from fluoro, chloro, bromo, methylthio,

- methylsulfinyl, methyl, ethyl, isopropyl, tert-butyl,
 isobutyl, pentyl, hexyl, cyano, fluoromethyl,
 difluoromethyl, trifluoromethyl, chloromethyl,
 dichloromethyl, trichloromethyl, pentafluoroethyl,
 5 heptafluoropropyl, difluorochloromethyl,
 dichlorofluoromethyl, difluoroethyl, difluoropropyl,
 dichloroethyl, dichloropropyl, hydroxyl, methoxy,
 methylenedioxy, ethoxy, propoxy, n-butoxy,
 hydroxymethyl, hydroxyethyl and trifluoromethoxy;
 10 wherein R⁷ is methyl or amino; and wherein R⁸ is a
 radical selected from hydrido, methylsulfonyl, fluoro,
 chloro, bromo, methylthio, methyl, ethyl, isopropyl,
 tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl,
 methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl,
 15 tert-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl,
 isobutoxycarbonyl, pentoxycarbonyl, fluoromethyl,
 difluoromethyl, trifluoromethyl, chloromethyl,
 dichloromethyl, trichloromethyl, pentafluoroethyl,
 heptafluoropropyl, difluorochloromethyl,
 20 dichlorofluoromethyl, difluoroethyl, difluoropropyl,
 dichloroethyl, dichloropropyl, hydroxyl, methoxy,
 methylenedioxy, ethoxy, propoxy, n-butoxy,
 hydroxymethyl, hydroxyethyl, methoxymethyl,
 ethoxymethyl, trifluoromethoxy, amino, methylamino, N,N-
 25 dimethylamino, phenylamino and nitro; or a
 pharmaceutically-acceptable salt thereof.

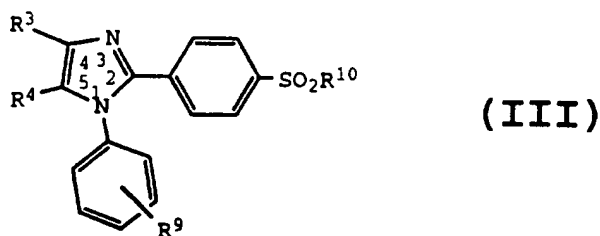
7. Compound of Claim 6 selected from compounds, and their pharmaceutically acceptable salts, of the group consisting of

- 30 2-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-
 (trifluoromethyl)-1H-imidazole;
 4-[2-(4-fluorophenyl)-4-(trifluoromethyl)-1H-imidazol-
 1-yl]benzenesulfonamide;
 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-
 35 (trifluoromethyl)-1H-imidazole;
 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-
 1-yl]benzenesulfonamide;

- 4-[2-(3,4-difluorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 2-(2-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 5 2-(3-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 4-[2-(2-fluorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 2-(4-fluoro-3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 10 2-(3-chloro-4-(N,N-dimethylamino)phenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 4-[2-(3-fluorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 15 2-(3-fluoro-4-(N,N-dimethylamino)phenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 2-(3-bromophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 20 2-(3-nitrophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 4-[2-(4-chloro-3-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 25 4-[2-(3,5-difluoro-4-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 30 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;
- 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;
- 35 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

- 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;
- 5 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 4-[2-(4-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 10 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(3-fluoro-4-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 15 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 20 2-(3,5-difluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 25 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 1-[4-(methylsulfonyl)phenyl]-2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 30 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide; and
- 35 2-(2-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole.

8. A compound of Formula III



(III)

- 5 wherein R³ is a radical selected from hydrido, alkyl, haloalkyl, aralkyl, heterocycloalkyl, acyl, cyano, alkoxy, alkylthio, alkylthioalkyl, alkylsulfonyl, cycloalkylthio, cycloalkylthioalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, cycloalkyloxy, cycloalkyloxyalkyl, haloalkylsulfonyl, arylsulfonyl, halo, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocycloalkylcarbonyl, cyanoalkyl, azidoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-alkyl-N-arylaminoalkyl, carboxyalkyl, 10 alkoxyalkyl, alkoxyalkyl, haloalkylcarbonyl, aminocarbonyl, N-alkylaminocarbonylalkyl, heteroarylalkoxyalkyl, heteroarylalkoxyalkyl, heteroarylthioalkyl, aralkoxy, aralkylthio, heteroaralkoxy, heteroaralkylthio, heteroarylalkylthioalkyl, heteroarylalkoxy, heteroarylthio, arylthioalkyl, arylalkoxyalkyl, arylthio, arylalkoxy, aralkylthioalkyl, aralkoxyalkyl, aryl and heteroaryl; wherein the aryl and heteroaryl radicals are optionally substituted at a substitutable position with one or more 25 radicals selected from halo, alkylthio, alkylsulfinyl, alkyl, cyano, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl and haloalkoxy; wherein R⁴ is a radical selected from hydrido, alkyl and fluoro; wherein R⁹ is one or more radicals selected from hydrido, halo, alkyl, haloalkyl, alkoxy, amino, haloalkoxy, cyano, carboxyl, hydroxyl, hydroxyalkyl, alkoxyalkyl, alkylamino, nitro and 30 alkylthio; and wherein R¹⁰ is a radical selected from

alkyl, haloalkyl and amino; or a pharmaceutically-acceptable salt thereof.

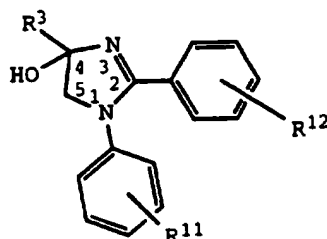
9. Compound of Claim 8 wherein R³ is a radical selected from hydrido, lower alkyl, lower haloalkyl, lower aralkyl, lower heterocycloalkyl, lower heteroaralkyl, acyl, cyano, lower alkoxy, lower alkylthio, lower alkylsulfonyl, phenylsulfonyl, lower haloalkylsulfonyl, halo, lower hydroxyalkyl, lower alkoxyalkyl, lower alkylcarbonyl, lower haloalkylcarbonyl, phenylcarbonyl, lower aralkylcarbonyl, lower cyanoalkyl, lower azidoalkyl, lower alkylaminoalkyl, lower N-arylaminoalkyl, lower N-alkyl-N-arylaminoalkyl, lower carboxyalkyl, lower alkoxycarbonylalkyl, lower alkoxycarbonyl, lower alkylthioalkyl, aminocarbonyl, lower alkylaminocarbonylalkyl, lower aralkoxy, lower aralkylthio, lower heteroaralkoxy, lower heteroaralkylthio, lower heteroarylalkoxyalkyl, lower heteroarylalkylthioalkyl, lower heteroaryloxyalkyl, lower heteroarylthio, lower arylthioalkyl, lower aryloxyalkyl, lower arylthio, lower aryloxy, lower aralkylthioalkyl, lower aralkoxyalkyl, aryl selected from phenyl and naphthyl, 5 or 6 membered heteroaryl, wherein the aryl and heteroaryl radicals are optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, cyano, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl and lower haloalkoxy; wherein R⁴ is a radical selected from hydrido, lower alkyl and fluoro; wherein R⁹ is a radical selected from hydrido, halo, lower alkyl, lower haloalkyl, lower alkoxy, amino, lower haloalkoxy, cyano, carboxyl, hydroxyl, lower hydroxyalkyl, lower alkoxyalkyl, lower alkylamino, nitro and lower alkylthio; and wherein R¹⁰ is a radical selected from

lower alkyl, lower haloalkyl and amino; or a pharmaceutically-acceptable salt thereof.

10. Compound of Claim 9 wherein R³ is a radical selected from hydrido, methyl, ethyl, isopropyl, tert-butyl, isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, benzyl, phenylethyl, phenylpropyl, furylmethyl, morpholinomethyl, pyrrolidinylmethyl, piperazinylmethyl, piperidinylmethyl, pyridylmethyl, thienylmethyl, formyl, cyano, methoxy, ethoxy, propoxy, n-butoxy, methylthio, ethylthio, methylsulfonyl, phenylsulfonyl, trifluoromethylsulfonyl, fluoro, chloro, bromo, hydroxymethyl, hydroxyethyl, methoxymethyl, ethoxymethyl, methylthiomethyl, benzyloxy, benzylthio, methylcarbonyl, phenylcarbonyl, trifluoromethylcarbonyl, difluoromethylcarbonyl, fluoromethylcarbonyl, benzylcarbonyl, cyanomethyl, cyanobutyl, azidomethyl, methylaminomethyl, N-phenylaminomethyl, N-methyl-N-phenylaminomethyl, acetyl, propanoyl, butanoyl, methoxycarbonylmethyl, ethoxycarbonylethyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, propoxycarbonyl, aminocarbonyl, methylaminocarbonylmethyl, pyridyloxy, pyridylthio, phenyloxy, 4-chlorophenoxy, furylmethoxy, furylmethylthio, thienylmethoxy, quinolylmethoxy, pyridylmethoxy, 5-phenylpyridyl-2-methoxy, thienylmethylthio, pyridylmethylthio, quinolylmethoxymethyl, furylbutoxyethyl, pyridyloxymethyl, pyridylmethoxymethyl, thienyloxyhexyl, thienylthiomethyl, pyridylthiohexyl, furyloxymethyl, furylmethylthiomethyl, quinolylmethylthioethyl, phenylthiomethyl, phenyloxymethyl, 4-chlorophenyloxymethyl, benzyloxymethyl, 4-

- methoxybenzyloxymethyl, naphthyl, phenyl, thienyl, furyl, pyridyl, wherein the thienyl, furyl, pyridyl and phenyl radicals are optionally substituted at a substitutable position with one or more radicals
- 5 selected from fluoro, chloro, bromo, methylthio, methylsulfinyl, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, pentyl, hexyl, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl,
- 10 heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, *n*-butoxy, hydroxymethyl, hydroxyethyl and trifluoromethoxy;
- 15 wherein R⁴ is a radical selected from hydrido, methyl, ethyl and fluoro; wherein R⁹ is a radical selected from hydrido, fluoro, chloro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl,
- 20 heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, methoxy, ethoxy, isopropoxy, *tert*-butoxy, propoxy, butoxy, isobutoxy, pentoxy, methylenedioxy, amino, trifluoromethoxy, cyano,
- 25 carboxyl, hydroxyl, nitro, hydroxymethyl, methoxymethyl, ethoxymethyl, methylamino, methylthio, ethylthio, propylthio and butylthio; and wherein R¹⁰ is methyl, fluoromethyl or amino, or a pharmaceutically-acceptable
- 30 salt thereof.

11. A compound of Formula IV



(IV)

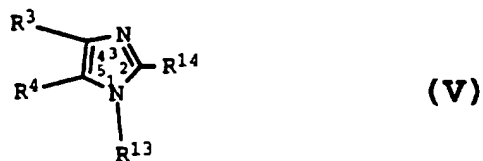
wherein R³ is selected from alkyl, haloalkyl, alkylsulfonylalkyl, cycloalkylthioalkyl, alkoxy carbonyl, aralkoxyalkyl, aryloxyalkyl, arylthioalkyl, N-aryl-N-alkylaminoalkyl, heteroarylalkoxyalkyl, heterocyclocarbonyl, heteroaryloxyalkyl, N-alkoxy-N-alkylaminocarbonyl, heteroaralkylthioalkyl, heteroarylthioalkyl and aryl optionally substituted at a substitutable position with halo, alkoxy and haloalkoxy; and wherein R¹¹ and R¹² are independently selected from hydrido, halo, alkyl, haloalkyl, alkoxy, alkylsulfonyl, haloalkylsulfonyl and sulfamyl; or a pharmaceutically-acceptable salt thereof.

12. Compound of Claim 11 wherein R³ is selected from lower alkyl, lower haloalkyl, lower aralkoxyalkyl, lower aryloxyalkyl, lower alkoxy carbonyl, lower arylthioalkyl, lower heteroaralkylthioalkyl, lower heteroarylthioalkyl, lower N-aryl-N-alkylaminoalkyl, lower heteroarylalkoxyalkyl and aryl selected from naphthyl, phenyl and biphenyl, wherein the aryl radical is optionally substituted at a substitutable position with halo, lower alkoxy and lower haloalkoxy; and wherein R¹¹ and R¹² are independently selected from hydrido, halo, lower alkyl, lower haloalkyl, lower alkoxy, lower alkylsulfonyl, lower haloalkylsulfonyl and sulfamyl; or a pharmaceutically-acceptable salt thereof.

13. Compound of Claim 12 wherein R³ is selected from methyl, ethyl, isopropyl, tert-butyl, isobutyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, ethoxycarbonyl, methoxycarbonyl, benzyloxymethyl, phenylthiomethyl, pyridylthiomethyl, pyridylmethylthiomethyl, phenyloxymethyl, 4-chlorophenyloxymethyl, N-phenyl-N-methylaminomethyl,

quinolyloxymethyl and aryl selected from naphthyl and phenyl, wherein the aryl radical is optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methoxy, ethoxy, isopropoxy, tert-butoxy, propoxy, butoxy, isobutoxy, pentoxy, methylenedioxy and trifluoromethoxy; and wherein R¹¹ and R¹² are independently selected from hydrido, fluoro, chloro, bromo, iodo, methyl, ethyl, isopropyl, tert-butyl, isobutyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, methoxy, ethoxy, isopropoxy, tert-butoxy, propoxy, butoxy, isobutoxy, pentoxy, methylenedioxy, methylsulfonyl, fluoromethylsulfonyl and sulfamyl; or a pharmaceutically-acceptable salt thereof.

14. A compound of Formula V



20

wherein R³ is a radical selected from hydrido, alkyl, haloalkyl, aralkyl, heterocycloalkyl, heteroaralkyl, acyl, cyano, alkoxy, alkylthio, alkylthioalkyl, alkylsulfonyl, cycloalkylthio, cycloalkylthioalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, haloalkylsulfonyl, arylsulfonyl, halo, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocyclocarbonyl, cyanoalkyl, aminoalkyl, alkylaminoalkyl, N-aryl aminoalkyl, N-alkyl-N-aryl aminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, haloalkylcarbonyl, carboxyl, aminocarbonyl, alkylaminocarbonyl, alkylaminocarbonylalkyl, heteroarylalkoxyalkyl,

35

heteroaryloxyalkyl, heteroarylthioalkyl, aralkoxy,
aralkylthio, heteroaralkoxy, heteroaralkylthio,
heteroarylalkylthioalkyl, heteroaryloxy,
heteroarylthio, arylthioalkyl, aryloxyalkyl, arylthio,
5 aryloxy, aralkylthioalkyl, aralkoxyalkyl, aryl and
heteroaryl; wherein R^4 is a radical selected from
hydrido, alkyl and halo; and wherein R^{13} and R^{14} are
independently selected from aryl and heterocyclo,
wherein R^{13} and R^{14} are optionally substituted at a
10 substitutable position with one or more radicals
independently selected from alkylsulfonyl,
aminosulfonyl, halo, alkylthio, alkyl, cyano, carboxyl,
alkoxycarbonyl, haloalkyl, hydroxyl, alkoxy,
hydroxyalkyl, alkoxyalkyl, haloalkoxy, amino,
15 alkylamino, arylamino and nitro; provided at least one
of R^{13} and R^{14} is aryl substituted with alkylsulfonyl or
aminosulfonyl; or a pharmaceutically-acceptable salt
thereof.

15. Compound of Claim 14 wherein R^3 is a radical
20 selected from hydrido, lower alkyl, lower haloalkyl,
lower aralkyl, lower heterocycloalkyl, lower
heteroaralkyl, acyl, cyano, lower alkoxy, lower
alkylthio, lower alkylsulfonyl, phenylsulfonyl, lower
haloalkylsulfonyl, halo, lower hydroxyalkyl, lower
25 alkoxyalkyl, lower alkylcarbonyl, lower
haloalkylcarbonyl, phenylcarbonyl, lower
aralkylcarbonyl, lower cyanoalkyl, lower aminoalkyl,
lower alkylaminoalkyl, lower N-arylaminalkyl, lower N-
alkyl-N-arylaminalkyl, lower carboxyalkyl, lower
30 alkoxyalkyl, lower alkoxyalkyl, carboxyl,
lower alkylthioalkyl, aminocarbonyl, lower
alkylaminocarbonyl, lower alkylaminocarbonylalkyl,
lower aralkoxy, lower aralkylthio, lower
heteroaralkoxy, lower heteroaralkylthio, lower
35 heteroarylalkoxyalkyl, lower heteroarylalkylthioalkyl,
lower heteroaryloxyalkyl, lower heteroarylthioalkyl,
lower heteroaryloxy, lower heteroarylthio, lower

- arylthioalkyl, lower aryloxyalkyl, lower arylthio, lower aryloxy, lower aralkylthioalkyl, lower aralkoxyalkyl, aryl selected from phenyl and naphthyl, 5 or 6 membered heteroaryl, wherein the aryl and
- 5 heteroaryl radicals are optionally substituted at a substitutable position with one or more radicals selected from halo, lower alkylthio, lower alkylsulfinyl, lower alkyl, cyano, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl and lower
- 10 haloalkoxy; wherein R^4 is a radical selected from hydrido, lower alkyl and halo; and wherein R^{13} and R^{14} are independently selected from phenyl and heteroaryl, wherein R^{13} and R^{14} are optionally substituted at a substitutable position with one or more radicals
- 15 independently selected from lower methylsulfonyl, aminosulfonyl, lower alkylthio, lower alkyl, lower haloalkyl, lower alkoxy, lower hydroxyalkyl, lower alkoxyalkyl, and lower haloalkoxy; or a pharmaceutically-acceptable salt thereof.
- 20 16. Compound of Claim 15 wherein R^3 is a radical selected from hydrido, methyl, ethyl, isopropyl, tert-butyl, isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl,
- 25 heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, benzyl, phenylethyl, phenylpropyl, furylmethyl, morpholinomethyl, pyrrolidinylmethyl, piperazinylmethyl,
- 30 piperidinylmethyl, pyridylmethyl, thienylmethyl, formyl, cyano, methoxy, ethoxy, propoxy, n-butoxy, methylthio, ethylthio, isopropylthio, methylsulfonyl, phenylsulfonyl, trifluoromethylsulfonyl, fluoro, chloro, bromo, hydroxymethyl, hydroxyethyl,
- 35 methoxymethyl, ethoxymethyl, methylthiomethyl, isopropylthiomethyl, cyclohexylthiomethyl, benzyloxy, benzylthio, methylcarbonyl, ethylcarbonyl,

phenylcarbonyl, trifluoromethylcarbonyl,
difluoromethylcarbonyl, fluoromethylcarbonyl,
benzylcarbonyl, pyrrolidinylcarbonyl, cyanomethyl,
cyanobutyl, aminomethyl, methylaminomethyl, N-
5 phenylaminomethyl, N-methyl-N-phenylaminomethyl,
acetyl, propanoyl, butanoyl, methoxycarbonylmethyl,
ethoxycarbonylethyl, methoxycarbonyl, ethoxycarbonyl,
isopropoxycarbonyl, tert-butoxycarbonyl,
propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl,
10 pentoxycarbonyl, carboxyl, carboxymethyl,
carboxypropyl, aminocarbonyl, methylaminocarbonyl, N,N-
diethylaminocarbonyl, N-methoxy-N-methylaminocarbonyl,
methylaminocarbonylmethyl, pyridyloxy, pyridylthio,
phenyloxy, 4-chlorophenoxy, furylmethoxy,
15 furylmethylthio, thienylmethoxy, quinolylmethoxy,
pyridylmethoxy, 5-phenylpyridyl-2-methoxy,
thienylmethylthio, pyridylmethylthio,
quinolylmethoxymethyl, furylbutoxyethyl,
pyridyloxymethyl, pyridylmethoxymethyl,
20 thienyloxyhexyl, thienylthiomethyl, pyridylthiohexyl,
furyloxymethyl, furylmethylthiomethyl,
quinolylmethylthioethyl, phenylthiomethyl, 2-
chlorophenylthiomethyl, 2,6-dichlorophenylthiomethyl,
4-methylphenylthiomethyl, 2-isopropylphenylthiomethyl,
25 2-methylphenylthiomethyl, phenyloxymethyl, 4-
chlorophenyloxymethyl, 4-methylphenyloxymethyl,
benzyloxymethyl, 4-methoxybenzyloxymethyl, naphthyl,
phenyl, thienyl, furyl, pyridyl, wherein the thienyl,
furyl, pyridyl and phenyl radicals are optionally
30 substituted at a substitutable position with one or
more radicals selected from fluoro, chloro, bromo,
methylthio, methylsulfinyl, methyl, ethyl, isopropyl,
tert-butyl, isobutyl, pentyl, hexyl, cyano,
fluoromethyl, difluoromethyl, trifluoromethyl,
35 chloromethyl, dichloromethyl, trichloromethyl,
pentafluoroethyl, heptafluoropropyl,
difluorochloromethyl, dichlorofluoromethyl,

- difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, hydroxymethyl, hydroxyethyl and trifluoromethoxy; wherein R⁴ is a radical selected from hydrido, methyl, ethyl, fluoro, chloro and bromo; and wherein R¹³ and R¹⁴ is selected from phenyl, imidazolyl, thienyl, thiazolyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazinyl, pyrimidinyl, quioliny, indolylbenzimidazolyl, pyrazolyl and pyridyl, wherein R¹³ and R¹⁴ are optionally substituted at a substitutable position with one or more radicals independently selected from methylsulfonyl, aminosulfonyl, fluoromethylsulfonyl, difluoromethylsulfonyl, fluoro, chloro, bromo, methylthio, methylsulfinyl, methyl, ethyl, isopropyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, hydroxymethyl, hydroxyethyl, methoxymethyl, ethoxymethyl, trifluoromethoxy, amino, methylamino, N,N-diethylamino, phenylamino and nitro; or a pharmaceutically-acceptable salt thereof.
17. Compound of Claim 16 wherein R³ is a radical selected from hydrido, methyl, ethyl, isopropyl, tert-butyl, isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, and dichloropropyl; wherein R⁴ is

hydrido; wherein R¹³ is phenyl optionally substituted with methylsulfonyl or aminosulfonyl; and wherein R¹⁴ is selected from imidazolyl, thienyl, thiazolyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrimidinyl, quiolinyl, indolyl, benzimidazolyl, pyrazolyl and pyridyl, wherein R¹⁴ is optionally substituted at a substitutable position with one or more radicals independently selected from methylthio, methyl, ethyl, isopropyl, tert-butyl, isobutyl, pentyl, hexyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, hydroxymethyl, hydroxyethyl, methoxymethyl, ethoxymethyl, and trifluoromethoxy; or a pharmaceutically-acceptable salt thereof.

18. Compound of Claim 17 selected from compounds, and their pharmaceutically acceptable salts, of the group consisting of
- 1-methyl-3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]-1H-indole;
 - 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
 - 2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]thiophene;
 - 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]thiophene;
 - 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
 - 2-methyl-3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
 - 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
 - 3-fluoro-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

- 3-chloro-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
4-[2-(5-fluoropyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
5 4-[2-(5-chloropyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
5-methyl-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
4-methyl-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
10 2-methoxy-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
5-methoxy-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
15 4-methoxy-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
2-chloro-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
5-chloro-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
20 4-chloro-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
2-fluoro-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
25 4-fluoro-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
4-fluoro-2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
4-[2-(5-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
30 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
4-[2-(6-methoxypyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
35 4-[2-(5-methoxy-pyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

- 4-[2-(4-methoxypyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(6-chloropyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 5 4-[2-(5-chloropyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-chloropyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(6-fluoropyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 10 4-[2-(5-fluoropyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(4-fluoropyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 15 3-methoxy-5-[1-[4-(methanesulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 3-[4-methyl-1-[4-(methanesulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 3-[4-[4-(fluorophenyl)-1-[4-(methanesulfonyl)phenyl]-1H-imidazol-2-yl]pyridine;
- 20 5-[1-[4-(methanesulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-(methylthio)pyridine;
- 3-[4-(difluoromethyl)-1-[4-(methanesulfonyl)phenyl]-1H-imidazol-2-yl]pyridine;
- 25 4-[2-(5-methoxypyridine-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[4-methyl-2-(3-pyridinyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(pyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 30 4-[4-(4-fluorophenyl)-2-(3-pyridinyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-[6-(methylthio)pyridin-3-yl]-4-trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 35 4-[4-(difluoromethyl)-2-(3-pyridinyl)-1H-imidazol-1-yl]benzenesulfonamide;

- 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
5 2-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
2-methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
10 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
3-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
15 2-methoxy-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine; and
2-[4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine.

20 19. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 1; or a pharmaceutically-acceptable salt thereof.

20. A pharmaceutical composition comprising a
25 therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 4; or a pharmaceutically-acceptable salt thereof.

21. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said
30 compound selected from a family of compounds of Claim 5; or a pharmaceutically-acceptable salt thereof.

22. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said
compound selected from a family of compounds of Claim
35 6; or a pharmaceutically-acceptable salt thereof.

23. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said

compound selected from a family of compounds of Claim 7; or a pharmaceutically-acceptable salt thereof.

24. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said
5 compound selected from a family of compounds of Claim 8; or a pharmaceutically-acceptable salt thereof.

25. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said
10 compound selected from a family of compounds of Claim 11; or a pharmaceutically-acceptable salt thereof.

26. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said
compound selected from a family of compounds of Claim 14; or a pharmaceutically-acceptable salt thereof.

15 27. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said
compound selected from a family of compounds of Claim 15; or a pharmaceutically-acceptable salt thereof.

20 28. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said
compound selected from a family of compounds of Claim 16; or a pharmaceutically-acceptable salt thereof.

25 29. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said
compound selected from a family of compounds of Claim 17; or a pharmaceutically-acceptable salt thereof.

30 30. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said
compound selected from a family of compounds of Claim 18; or a pharmaceutically-acceptable salt thereof.

31. A method of treating inflammation or an inflammation-associated disorder in a subject, said
method comprising administering to the subject having or susceptible to said disorder, a therapeutically-
35 effective amount of a compound of Claim 1; or a pharmaceutically-acceptable salt thereof.

32. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 4; or a pharmaceutically-acceptable salt thereof.

33. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 5; or a pharmaceutically-acceptable salt thereof.

34. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 6; or a pharmaceutically-acceptable salt thereof.

35. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 7; or a pharmaceutically-acceptable salt thereof.

36. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 8; or a pharmaceutically-acceptable salt thereof.

37. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 11; or a pharmaceutically-acceptable salt thereof.

38. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 14; or a
5 pharmaceutically-acceptable salt thereof.

39. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having
10 or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 15; or a pharmaceutically-acceptable salt thereof.

40. A method of treating inflammation or an inflammation-associated disorder in a subject, said
15 method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 16; or a pharmaceutically-acceptable salt thereof.

41. A method of treating inflammation or an inflammation-associated disorder in a subject, said
20 method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 17; or a pharmaceutically-acceptable salt thereof.

42. A method of treating inflammation or an inflammation-associated disorder in a subject, said
25 method comprising administering to the subject having or susceptible to said disorder, a therapeutically-effective amount of a compound of Claim 18; or a pharmaceutically-acceptable salt thereof.
30

43. The method of Claim 31 for use in treatment of inflammation.

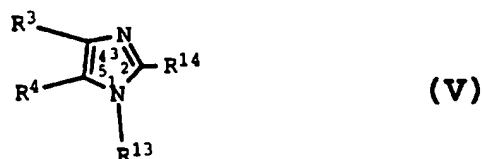
44. The method of Claim 31 for use in treatment of an inflammation-associated disorder.

35 45. The method of Claim 44 wherein the inflammation-associated disorder is arthritis.

46. The method of Claim 44 wherein the inflammation-associated disorder is pain.

47. The method of Claim 44 wherein the inflammation-associated disorder is fever.

5 48. A process of making a compound of Formula V



or a pharmaceutically acceptable salt thereof,
 10 wherein R³ is a radical selected from hydrido, alkyl, haloalkyl, aralkyl, heterocycloalkyl, heteroaralkyl, acyl, cyano, alkoxy, alkylthio, alkylthioalkyl, alkylsulfonyl, cycloalkylthio, cycloalkylthioalkyl, cycloalkylsulfonyl,
 15 cycloalkylsulfonylalkyl, haloalkylsulfonyl, arylsulfonyl, halo, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocyclocarbonyl, cyanoalkyl, aminoalkyl, alkylaminoalkyl, N-aryl aminoalkyl, N-alkyl-N-
 20 aryl aminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, haloalkylcarbonyl, carboxyl, aminocarbonyl, alkylaminocarbonyl, alkylaminocarbonylalkyl, heteroarylalkoxyalkyl, heteroaryloxyalkyl, heteroarylthioalkyl, aralkoxy,
 25 aralkylthio, heteroaralkoxy, heteroaralkylthio, heteroarylalkylthioalkyl, heteroaryloxy, heteroarylthio, arylthioalkyl, aryloxyalkyl, arylthio, aryloxy, aralkylthioalkyl, aralkoxyalkyl, aryl and heteroaryl; wherein R⁴ is hydrido; and wherein R¹³ and
 30 R¹⁴ are independently selected from aryl and heterocyclo, wherein R¹³ and R¹⁴ are optionally substituted at a substitutable position with one or more radicals independently selected from
 35 aminosulfonyl, halo, alkylthio, alkyl cyano, carboxyl, alkoxycarbonyl, haloalkyl, hydroxyl, alkoxy,

hydroxyalkyl, alkoxyalkyl, haloalkoxy, amino, alkylamino, arylamino and nitro; provided at least one of R^{13} and R^{14} is aryl substituted with aminosulfonyl;

- 5 said method comprising the steps of treating a methyl sulfone with a base and an substituted trialkylsilane in an appropriate solvent to form a silylalkylsulfone, treating said silylalkylsulfone with an alkylammonium halide to form a sulfinic acid salt, and forming said
- 10 sulfonamide by treating the sulfinic acid salt with an aminating agent.

INTERNATIONAL SEARCH REPORT

Intern: Application No
PCT/US 95/09506

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D233/54 A61K31/415 C07D233/32 C07D233/90 C07D401/04
C07D403/04 C07D405/04 C07D409/04 C07D417/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | EP,A,0 554 829 (FUJISAWA PHARMACEUTICALS CO., LTD.) 11 August 1993 see page 30; claim 1 see page 29; example 29.3 see page 16, line 36 - line 52 ---- | 1-47 |
| A | EP,A,0 257 897 (FUJISAWA PHARMACEUTICALS CO., LTD.) 2 March 1988 cited in the application see page 63 - page 64; claim 1 see page 35; example 111 see page 3, line 5 - line 7 ----- | 1-47 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Δ* document member of the same patent family

Date of the actual completion of the international search

20 November 1995

Date of mailing of the international search report

29. 11. 95

Name and mailing address of the ISA

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Authorized officer

Fink, D

INTERNATIONAL SEARCH REPORT

In ternational application No.

PCT/US 95/09506

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 31-47 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/09506

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| EP-A-0554829 | 11-08-93 | AU-B- 663149 | 28-09-95 |
| | | AU-A- 3217493 | 12-08-93 |
| | | CA-A- 2088835 | 06-08-93 |
| | | CN-A- 1075959 | 08-09-93 |
| | | JP-A- 5246997 | 24-09-93 |
| | | ZA-A- 9300077 | 04-08-93 |
| ----- | | | |
| EP-A-0257897 | 02-03-88 | AU-B- 7682587 | 18-02-88 |
| | | JP-A- 63054369 | 08-03-88 |
| | | OA-A- 8647 | 30-11-88 |
| | | US-A- 4822805 | 18-04-89 |
| | | ZA-A- 8705790 | 15-02-88 |
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